Impulsive compulsive behaviours in Parkinson's disease: an observational, eye movement and neuropathological study

Thesis submitted in fulfilment of the degree of Doctor of Philosophy

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2019

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I, Pedro Melo Barbosa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:
Date:

Abstract

This thesis focuses on impulsive compulsive behaviours (ICBs) in Parkinson's disease (PD), behavioural complications that can arise in association with dopaminergic treatment.

Initially, the long-term outcome of ICBs was assessed, revealing that 58% of the patients remained symptomatic after 8 years of follow up. Reduction of dopaminergic treatment was effective in decreasing symptoms but did not guarantee long-term remission. The presence of ICBs was associated with depression and worse quality of life but it did not increase the risk of cognitive impairment.

Compulsive sexual behaviour in PD was found to be more frequent in males and associated with multiple ICBs and higher doses of levodopa when compared to other ICBs. The outcome of patients with dopamine dysregulation syndrome (DDS) until death was investigated in a brain bank cohort showing that half of the patients remained symptomatic and that remission was associated with lower levodopa dose at death. Punding in PD was associated with higher impulsivity and worse frontal function compared to other ICBs. Apomorphine infusion was found to be less likely to trigger or worsen ICBs in PD patients than other dopamine agonists in a retrospective analysis.

Automatic and voluntary saccadic eye movements of PD patients with ICBs (PD+ICB) were compared to PD patients without ICBs and healthy controls. PD+ICB had hypometric voluntary saccades and made a significantly higher number of direction errors in the anti-saccades task. Considering that ICBs are under-reported, this finding, if confirmed, could lead to the development of a novel way of identifying these abnormal behaviours.

Lastly, brain tissue from 24 PD patients with DDS were assessed for alpha-synuclein, tyrosine hydroxylase, and dopamine D2 and D3 receptors protein levels. Lower levels of alpha-synuclein were found in the nucleus accumbens of patients with ICBs suggesting a central role for this structure in the pathophysiology of ICBs.

Impact statement

Although nearly two decades have passed since the initial description of impulsive compulsive behaviours (ICBs) in Parkinson's disease (PD), little is known about the long-term prognosis and the pathophysiology of these disabling behavioural abnormalities.

The characteristic lack of insight that accompanies ICBs means that diagnosis often comes too late, when patients have incurred significant debt and personal relationships have been irreversibly affected. Benefits for clinical practice are likely to derive from the findings reported in this thesis. By showing that more than half of the patients remain symptomatic in the long-term, the need for close clinical vigilance is reinforced, even after patients have experienced remission of ICBs and, particularly, after increases in medication required for disease progression. Furthermore, the data shows that, despite the low remission rate, reduction of dopaminergic treatment is indeed an effective way to decrease the severity of ICBs, confirming this strategy as the gold standard treatment of these troubling behaviours.

The main points for the management of compulsive sexual behaviour (CSB) in PD are: dopamine agonists (DA) should be discontinued if possible; and patients using higher doses of levodopa should be carefully screened for CSB, considering its reported association with higher doses of levodopa. Data on the safety of apomorphine continuous infusion in patients with ICBs was provided, suggesting that this medication could be safely prescribed to patients with a previous history of ICBs, to patients who become handicapped after cessation of DA and to patients with active ICBs in an attempt to reduce other dopaminergic medications.

An insight into the mechanisms behind punding was provided. The finding that punding is associated with frontal dysfunction and higher impulsivity levels could aid future studies to unravel the cause of punding and perhaps contribute to the development of novel treatments.

A much-needed development in the field of ICBs in PD is the correct identification of patients who are at risk or who have already developed ICBs and lack insight. In this thesis, a novel way of identifying these behavioural abnormalities using anti-saccadic direction error was presented. The potential for anti-saccadic error rate to be a clinical marker for ICBs should be assessed in future studies. If confirmed, this finding has the potential to become an important compass to guide treatment choices in patients at risk of developing ICBs.

The post mortem study is one important step towards unravelling the pathophysiology of ICBs. Reduced alpha-synuclein load was found in the nucleus accumbens (NAc) of PD patients with ICBs. Dopamine overdose of the ventral striatum with a relatively preserved NAc could be an important mechanism behind ICBs. Benefits for both the field of ICBs in PD and drug addiction are likely to ensue considering the shared pathophysiological phenomena between these conditions.

Publications related to this thesis

Published manuscripts

Barbosa P, Lees AJ, Magee C, Djamshidian A, Warner TT. A Retrospective Evaluation of the Frequency of Impulsive Compulsive Behaviors in Parkinson's Disease Patients Treated with Continuous Waking Day Apomorphine Pumps. *Movement Disorders Clinical Practice,* 11;4(3):323-328, (2016).

Barbosa PM, Grippe T, Lees AJ, O'Sullivan SS, Djamshidian A, Warner TT. Compulsive sexual behaviour in Parkinson's disease is associated with higher doses of levodopa. *Journal of Neurology, Neurosurgery and Psychiatry*, 89(10)**:**1121-1123, (2018).

Barbosa P, Djamshidian A, Lees AJ, and Warner TT. The Outcome of Dopamine Dysregulation Syndrome in Parkinson's Disease: A Retrospective Postmortem Study. *Movement Disorders Clinical Practice*, 4;5(5):519-522, (2018).

Manuscripts under peer review

Barbosa P, Djamshidian A, O'Sullivan SS, de Pablo-Fernandez E, Korlipara P, Morris HR, Bhatia KP, Limousin P, Foltynie T, Lees AJ, Warner TT. The long-term outcome of impulsive compulsive behaviours in Parkinson's disease.

Barbosa P, O'Sullivan SS, Joyce E, Lees AJ, Warner TT, Djamshidian A. Cognitive and neuropsychiatric profile of patients with Parkinson's disease who exhibit punding.

Barbosa P, Kaski D, Lees AJ, Warner TT, Djamshidian A. Impaired saccadic suppression in Parkinson's disease patients with impulsive compulsive behaviours.

Manuscripts being prepared for publication

Barbosa P, Hapuarachchi B, Djamshidian A, Strand K, Lees AJ, Djamshidian A, de Silva R, Holton J, Warner TT. Impulsive compulsive behaviours in Parkinson's disease are associated with lower alpha-synuclein load and D3 receptor levels in the nucleus accumbens.

Declaration of collaborative work

Chapter 5: Dopamine dysregulation syndrome in Parkinson's disease is associated with lower alpha-synuclein load in the nucleus accumbens

Clinical data review and analysis were conducted by Pedro Barbosa. Microdissection of the nucleus accumbens, putamen and frontal cortex was performed by Mrs Linda Parsons and Mrs Geshanthi Hondhamuni. Tissue sections were cut, mounted on glass slides, and stained with haematoxylin and eosin and luxol fast blue by Pedro Barbosa. Alpha-synuclein and tyrosine hydroxylase staining was performed by Mrs Katherine Strand. Image analysis of alpha-synuclein and tyrosine hydroxylase immunoreactivity was conducted by Pedro Barbosa.

Protein preparation from brain tissue and quantification of sample protein for western immunoblotting were performed by Mrs Bimali Hapuarachchi. Immunoblot analysis of proteins was conducted mostly by Mrs Hapuarachchi with the help of Pedro Barbosa. Randomisation of samples, densitometry of immunoblots and data analysis by Pedro Barbosa. Prof Janice Holton conducted the staging of Lewy pathology and Alzheimer's disease neuropathological changes.

List of abbreviations

AIMS	Abnormal Involuntary Movement Scale
AS	Apathy Scale
BIS11	Barratt Impulsiveness Scale
BSA	Bovine serum albumin
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
COMTi	Catecol O-Methyltransferase inhibitors
CSB	Compulsive sexual behaviour
D1R	Dopamine D1 receptor
D2R	Dopamine D2 receptor
D3R	Dopamine D3 receptor
DA	Dopamine agonists
DAWS	Dopamine agonist withdrawal syndrome
DBS	Deep brain stimulation
DDS	Dopamine dysregulation syndrome
DLPFC	Dorsolateral prefrontal cortex
FAB	Frontal Assessment Battery
HADS	Hospital Anxiety and Depression Scale
HC	Healthy controls
ICBs	Impulsive compulsive behaviours
IMS	Industrial methylated spirit
LEDD	Levodopa equivalent daily dose
MAOi	Monoamine oxidase inhibitors
MoCA	Montreal Cognitive Assessment
NAc	Nucleus accumbens
NIA-AA	National Institute of Aging-Alzheimer's Association
NMS	Non-motor symptoms
PD	Parkinson's disease
PD+CSB	Patients with Parkinson's disease and compulsive sexual behaviour
PD-CSB	Patients with Parkinson's disease without compulsive sexual behaviour
PD+DDS	Patients with Parkinson's disease and dopamine dysregulation syndrome

PD-DDS	Patients with Parkinson's disease without dopamine dysregulation syndrome
PD+ICB	Patients with Parkinson's disease and impulsive compulsive behaviours
PD-ICB	Patients with Parkinson's disease without impulsive compulsive behaviours
PD+pu	Patients with Parkinson's disease and punding
PD+V1DDS/pu	Patients with Parkinson's disease and dopamine dysregulation syndrome and/or punding at visit 1
PD-V1DDS/pu	Patients with Parkinson's disease and impulsive compulsive behaviours other than dopamine dysregulation syndrome and punding at visit 1
PD+V2ICB	Patients with Parkinson's disease and active impulsive compulsive behaviours at visit 2
PD-V2ICB	Patients with Parkinson's disease who had experienced complete remission of impulsive compulsive behaviours by visit 2
PET	Positron emission tomography
QSBB	Queen Square Brain Bank for Neurological Disorders
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBD	REM sleep behaviour disorder
RBDq	REM Sleep Behaviour Disorder Questionnaire
RLS	Restless legs syndrome
ROI	Region of interest
SC	Superior colliculus
SF36	36-Item Short Form Survey
STN	Subthalamic nucleus
TBS	Tris buffered saline
TH	Tyrosine hydroxylase
UPDRS	Unified Parkinson's Disease Rating Scale
V1	Visit 1
V2	Visit 2

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Chapter 1: Impulsive compulsive behaviours in Parkinson's disease

1.1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative condition affecting approximately 1 to 2 individuals per 1000 population (Tysnes and Storstein, 2017). There is a significant age-related increase in the risk of developing PD. The prevalence of 0.3% in the general population increases from 1% of individuals with 60 years of age to approximately 3% of individuals with 80 years or older (Fahn et al., 2011a). Gender also appears to influence the risk as it has been shown that PD affects more men than women (Cantuti-Castelvetri et al., 2007).

The disease is characterized by loss of dopaminergic neurons in the substantia nigra and degeneration of the striatonigral pathways. Microscopically, the affected areas present with Lewy bodies and Lewy neurites, composed mainly of alpha-synuclein (Jellinger, 2011). Although the classical motor signs (rigidity, bradykinesia, tremor and postural instability) dominate the clinical picture, degeneration of other neuronal systems can result in a constellation of non-motor symptoms (NMS). NMS can be the presenting symptom in PD, tend to become more common as the disease progresses and have a negative impact in the quality of life of individuals with PD (Fahn et al., 2011a).

Most NMS can be classified as sensory symptoms, such as pain, restless legs syndrome (RLS) and hyposmia; or autonomic symptoms, like orthostatic hypotension, constipation, and urinary symptoms. Psychiatric and behavioural NMS include depression, anxiety, apathy, psychosis, cognitive impairment and impulsive compulsive behaviours (ICBs), poorly understood behavioural abnormalities associated with dopaminergic treatment (table 1 on page 17). ICBs are the central theme of this thesis and are described in detail in the next section.

Table 1. Common non-motor symptoms in Parkinson's disease	
Sensory symptoms	Pain, paraesthesia, numbness, burning sensation, akathisia, restless legs syndrome, hyposmia.
Autonomic symptoms	Urinary symptoms, sexual dysfunction, orthostatic hypotension, excessive salivation, constipation, excessive sweating, dysphagia, delayed gastric emptying.
Behavioural and psychiatric symptoms	Depression, anxiety, apathy, abulia, bradyphrenia, psychosis, hallucinations, personality changes, impulsive compulsive behaviours.
Other symptoms	Sleep fragmentation, sleep apnoea, REM sleep behaviour disorder, excessive daytime sleepiness, fatigue, cognitive impairment, confusion.

Common non-motor symptoms in Parkinson's disease according to domain.

The absence of a curative treatment and disease modifying drugs means that PD treatment has traditionally focused on using medication to reduce the striatal dopaminergic deficit and alleviate motor symptoms. With disease progression, the majority of patients develop motor fluctuations and complications that can make the management of the condition challenging. Although treatments such as infusion therapies and deep brain stimulation can provide additional benefit at the advanced stage, disability invariably accumulates as disease progresses with most patients reaching end stage disease after approximately 15 years of onset (Poewe, 2006).

1.2 Impulsive compulsive behaviours in Parkinson's disease

ICBs is an umbrella term used to describe behavioural abnormalities that can develop in PD patients in association with dopaminergic treatment. Some ICBs are characterised by high levels of impulsivity, i.e. failure to resist temptations and urges, such as compulsive sexual behaviour (CSB), pathological gambling, compulsive eating, and compulsive shopping; whereas others are associated with repetitive and/or compulsive behaviours, such as punding, a complex behavioural abnormality characterized by engagement in stereotyped non-goal oriented activities, hoarding behaviour, excessive hobbyism and the compulsive use of dopaminergic medication regardless of what is needed to achieve therapeutic benefit, also known as dopamine dysregulation syndrome (DDS) (Evans et al., 2004). Other less common ICBs that have been described in PD are: reckless generosity, compulsive smoking, reckless driving, aggression and walkabouts (Djamshidian et al., 2011a).

Since the initial description of DDS by Giovannoni and colleagues in 2000 (Giovannoni et al., 2000), clinical and scientific interest in ICBs has exponentially increased. Although in the past 18 years much has been learnt about the risk factors for ICBSs and its association with dopaminergic treatment, many questions remain unanswered, such as what causes ICBs, why some individuals are more susceptible than others, the prognosis and long-term outcome, and whether reduction of dopaminergic treatment is associated with long term remission.

1.2.1 Epidemiology

Since the initial description of DDS, reports from several authors have confirmed that ICBs are relatively common in PD. The largest study assessing the prevalence of ICBs was conducted in multiple centres across the US and Canada, whereby the authors analysed 3090 patients with PD receiving dopaminergic treatment and found that 14% had at least one of the following ICBs: CSB, pathological gambling, compulsive shopping and compulsive eating, with one quarter of them presenting with more than one behavioural addiction (Weintraub et al., 2010a). A similar prevalence had been reported in a previous study analysing 193 consecutive PD patients (Giladi et al., 2007).

After these initial publications, researchers have assessed populations of PD patients from different countries suggesting a significant variability in the prevalence of ICBs. Low prevalence has been reported in China (3.53%) (Fan et al., 2009), Shanghai (4.15%) (Wang et al., 2016), and Turkey (5.9%) (Kenangil et al., 2010), whereas higher prevalence has been reported in Brazil (18.4%) (Valenca et al., 2013), Japan (21.5%) (Tanaka et al., 2013), Malaya (23.5%) (Lim et al., 2011), France (25%) (Perez-Lloret et al., 2012a), Norway (30.4%) (Erga et al., 2017), Finland (34.8%) (Joutsa et al., 2012), and Denmark (35.9%) (Callesen et al., 2014). Cultural factors, different laws regarding gambling availability and the different methods used to diagnose ICBs are possible explanations for the variation seen in these figures. It is also important to consider the possibility of under-reporting of ICBs by patients and their family/carers due to lack of insight, concealment associated with the sensitive nature of some ICBs, and failure to associate the behaviour with PD.

The proportion of patients with ICBs in a specific population appears to remain stable over time as shown by a prospective observational study conducted in Italy. More than one thousand patients with PD were followed up for 2 years, showing that the prevalence of ICBs assessed by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) remained stable at baseline (34.2%), year 1 (34.8%) and year 2 (32.1%). The same was true for the proportion of patients with multiple ICBs, approximately 45%, which did not change between assessments (Antonini et al., 2017).

A few studies have assessed the occurrence of specific types of ICBs. Pathological gambling is defined as maladaptive gaming behaviour and its lifetime prevalence in PD patients on dopaminergic therapy varies between 3.4% and 6%, with slightly higher rates reported on individuals using dopamine agonists (DA) (7.2%) and lower rates reported in China and Korea (0.32% and 1.3% respectively) (Djamshidian et al., 2011b, Voon et al., 2006b). The lifetime prevalence of CSB in PD is estimated between 2 and 3.9% (Voon et al., 2006a, Weintraub et al., 2006, Weintraub et al., 2010a), and 7.4% of patients on DA (Nakum and Cavanna, 2016). Compulsive shopping can affect 0.7% (Voon et al., 2006a), 3.4% (Lee et al., 2010) and 5.7% (Weintraub et al., 2010a) of PD patients anytime during disease duration. Only one paper from the United States assessed the prevalence of compulsive eating, showing that it affects 4.3% of American PD patients (Weintraub et al., 2010a). DDS affects between 3.4 and 4.1% of PD patients on dopaminergic treatment (Djamshidian et al., 2011a, Giovannoni et al., 2000). Punding affects from 1.4% (Miyasaki et al., 2007) to 4.2% (Lee et al., 2010) of individuals with PD, up to 14% of patients on higher doses of dopamine replacement therapy (Evans et al., 2004). Hoarding behaviours is present in 28% of individuals with PD and ICBs and 3.5% of PD patients without ICBs (PD-ICB) (O'Sullivan et al., 2010b).

1.2.2 Risk factors and associated clinical features

Risk factors for developing ICBs include the use of dopaminergic medication, younger age at PD onset, higher novelty seeking personality trait, male sex, a personal or family history of addictive behaviours and a past or family history of depression (Averbeck et al., 2014). One study found a higher likelihood of developing ICBs in PD patients with preserved cognition, however the overall prevalence of ICBs reported was 8.1%, raising the possibility of underestimation (Poletti et al., 2013). Regarding the different types of ICBs, longer disease duration has been reported as a risk factor for DDS (Katzenschlager, 2011), and longer PD duration and the presence of dyskinesias as risk factors for punding (Yoo et al., 2015).

Dopaminergic therapy is the only modifiable risk factor for ICBs, after initiation of dopamine replacement therapy there is a cumulative increase in the risk of developing these behavioural abnormalities over time (Smith et al., 2015). Although levodopa has also been associated with the development of ICBs in PD, the most important risk factor is DA therapy (Weintraub et al., 2010a, Voon et al., 2007), as confirmed by several epidemiological studies assessing PD populations from different countries (Weintraub et al., 2010a, Giladi et al., 2007, Bastiaens et al., 2013, Weintraub et al., 2006). Hassan and colleagues assessed 321 PD patients on DA and found that 16% of them had ICBs, however if only patients on therapeutic doses of agonists were considered (defined by the authors as doses equal or higher than 2 mg of pramipexol or 6 mg of ropinirole daily) the number of individuals affected reached 24% (Hassan et al., 2011). Garcia-Ruiz and colleagues studied PD patients using DA for at least 6 months and reported an even higher prevalence of ICBs: 39% (Garcia-Ruiz et al., 2014). A similar prevalence was found in a prospective study that followed up PD patients for a maximum period of four years. Among 46 patients on DA, 39.1% developed ICBs after a mean period of 21 months (Bastiaens et al., 2013). Another study conducted with PD patients from three Latin American countries, Argentina, Colombia and Ecuador, reported an overall prevalence of ICBs of 27.45%, but among patients who received DA at some point, ICBs occurred in 34.7% (Ramirez Gomez et al., 2017). Two studies have reported an association between higher doses of DA and the development of ICBs in PD: a prospective study found a positive correlation between higher peak DA doses and ICBs (Bastiaens et al., 2013), and a recently published longitudinal study reported that larger doses and longer duration of DA use contributes to higher prevalence of ICBs (Corvol et al., 2018).

Research with animal models support the association between DA and ICBs. Ropinirole has been shown to increase risky behaviours in a rodent model of gambling behaviour (Tremblay et al., 2016) and pramipexole has been associated with risky choices in a rodent model of PD (Rokosik and Napier, 2012). The development of behavioural addictions in individuals using dopaminergic drugs for medical conditions other than PD is another factor corroborating this association. Among patients receiving treatment for RLS the prevalence of ICBs varies from 5 to 17% (Driver-Dunckley et al., 2007,

Pourcher et al., 2010, Cornelius et al., 2010), furthermore only RLS patients using dopaminergic medications develop behavioural addictions (Cornelius et al., 2010). ICBs have also been reported in patients using DA to treat pituitary adenomas (Martinkova et al., 2011), multiple system atrophy (Klos et al., 2005), progressive supranuclear palsy (O'Sullivan et al., 2010a) and tetrahydrobiopterin deficiency (Porta et al., 2016).

Different types of DA may carry a lower risk of triggering ICBs. Apomorphine is a dopamine agonist which binds preferentially to dopamine D1 receptors (D1R) and dopamine D2 receptors (D2R), resembling more levodopa in its pharmacokinetic properties compared to other agonists. No randomized clinical trials have assessed apomorphine's proclivity to induce ICBs, but initial reports point to a better risk profile compared to other DA (Todorova et al., 2015, Martinez-Martin et al., 2014). Rotigotine is a DA that is delivered through a cutaneous patch. Although some authors have reported a lower prevalence of ICBs on patients using this drug compared to pramipexole and ropinirole (Garcia-Ruiz et al., 2014, Todorova et al., 2013, Antonini et al., 2016), randomized clinical trials are needed to provide a definitive answer to this question.

Specific types of ICBs might be associated with different types of dopaminergic medication. Pathological gambling and compulsive eating appear to be much more common with oral DA therapy (Djamshidian et al., 2011b), whereas DDS is more commonly seen with levodopa (Katzenschlager, 2011) and punding with drugs that stimulate D1R and D2R (Fasano and Petrovic, 2010). Data on the propensity of other PD medications to induce ICBs originate mainly from case reports and observational studies. Although both amantadine and monoamine oxidase inhibitors (MAOi) appear to be safer than DA, contradictory data is available on the propensity of amantadine to induce ICBs and case reports of ICBs in patients using MAOi have been published (Averbeck et al., 2014).

Most of the previously cited prevalence studies confirm previous findings that individuals who develop PD at an earlier age are at increased risk of developing ICBs (Weintraub et al., 2010a). In fact, ICBs have been reported to affect up to

58.3% of individuals with onset of PD before the age of 45 (Vela et al., 2016). Sex can influence the development of specific types of ICBs. CSB has been more frequently reported in males, whereas females more commonly develop compulsive shopping and compulsive eating (Djamshidian et al., 2011a).

The data on the association between REM sleep behaviour disorder (RBD) and ICBs is contradictory, which could be a consequence of the different methods used by researchers to diagnose both conditions. Kim and colleagues studied 994 patients for the presence of RBD and found a higher incidence of ICBs in these individuals, however the RBD group was on higher levodopa equivalent daily dosage (Kim et al., 2014). Whilst another group has also found a positive association between RBD and ICBs in PD patients (Fantini et al., 2015), two studies with smaller sample sizes have not found such association (Postuma et al., 2008, Romenets et al., 2012). Another study, the only one that used video-polysomnography, found no association between RBD and ICBs (Bayard et al., 2014). Nonetheless, sleep problems are common in patients with PD and ICBs and can be a consequence of increased impulsivity levels or the putative association between ICBs and RBD (Djamshidian et al., 2015).

Impulsivity predating PD onset may be a risk factor for ICBs (Weintraub et al., 2006) as shown by a study from Italy. The authors identified impulse control disorders in 17.5% of drug-naïve PD patients, similar to healthy controls, showing that subclinical impulsivity can be common in PD and could, theoretically, contribute to the development of ICBs (Antonini et al., 2011). The side of onset of PD symptoms has been shown to influence novelty seeking personality trait. Harris and colleagues found that patients with right-onset PD using DA exhibited higher levels of novelty seeking compared to patients with PD onset on the left side, suggesting that the former group is at higher risk of developing impulse control disorders. The authors postulated that higher premorbid dopamine levels in the left striatum could contribute to excessive stimulation of its ventral part by dopaminergic drugs and lead to the development of ICBs (Harris et al., 2015).

1.2.3 Cognitive, behavioural and neuropsychiatric features

PD patients with ICBs (PD+ICB) have worse quality of life (Alvarado-Bolanos et al., 2015) and more functional impairment (Voon et al., 2011b) when compared to PD patients with no behavioural addictions. Moreover, carers of individuals with PD report greater burden of care when ICBs are present (Leroi et al., 2012b). Not only do PD+ICB tend to suffer more from depression (Phu et al., 2014) and anxiety (Voon et al., 2011b), but depression is more severe when multiple ICBs are present (Wu et al., 2015). Anxiety and worse autonomic and cognitive functions can be present in PD+ICB at the time of PD diagnosis, before the development of behavioural addictions (Ricciardi et al., 2018). Greater obsessive-compulsive symptoms have been reported in PD+ICB compared to PD-ICB (Voon et al., 2011b). Patients with PD and DDS display more neuropsychiatric symptoms such as depression, irritability, and disinhibition, when compared to PD without DDS (Cilia et al., 2014). Alexithymia, a personality trait characterised by difficulty in processing emotions, appears to be more common in PD compared to healthy individuals and may contribute to the development of ICBs (Ricciardi et al., 2015).

Motor and reflection impulsivity, with consequences on decision making, have been reported in PD+ICB. In the beads task participants are asked to guess from which of two cups coloured beads are being drawn. The cups have different proportions of beads of two colours and participants are charged for each bead drawn. Rewards are given for correct guesses and wrong guesses are penalised (Averbeck et al., 2014). This task has been used by Djamshidian and colleagues to show that PD+ICB have reflection impulsivity. In essence, these individuals gather less information before making a decision, when compared to PD-ICB and healthy controls (Djamshidian et al., 2012b). Reflection impulsivity has also been described in PD patients being treated with DA that have not developed ICBs (Djamshidian et al., 2013). Other abnormalities on decision making have been reported, with PD+ICB showing decreased learning from negative feedback and increased learning to positive feedback in OFF medication, and increased learning to negative feedback when ON medication (Djamshidian et al., 2010, Djamshidian et al., 2012a), the opposite of what has been found in PD-ICB (Frank et al., 2004).

The Kirby questionnaire tests participants' preference for immediate or delayed small, medium or large monetary rewards and has been used as a measure of impulsivity and delay discounting, preference for smaller rewards over delayed larger rewards. Housden and collaborators found that PD+ICB have highly elevated delay discounting, suggesting that ICBs are a consequence of stronger preference for immediate over future recompenses rather than an overvaluation of rewards (Housden et al., 2010), although inappropriate subjective estimation of rewards has also been demonstrated in PD+ICB (Pineau et al., 2016). Interestingly, delay discounting has also been reported in PD-ICB receiving treatment with DA (Milenkova et al., 2011) and in non-medicated PD patients without overt ICBs, raising the question whether impulsive decision making occur as part of the disease or as a consequence of the use of DA (Al-Khaled et al., 2015). Risk taking behaviour has been associated with dopaminergic therapy in PD patients (Djamshidian et al., 2010), and has been reported in patients with pathological gambling (Djamshidian et al., 2010) and compulsive shopping using DA (Voon et al., 2011a).

Contradictory data has been published on executive dysfunction in PD+ICB. While poor performance on working memory tasks has been described in comparison to PD-ICB (Djamshidian et al., 2010), comparable performance on the Stroop test has been reported (Djamshidian et al., 2011c). Cognitive function does not deteriorate faster in PD+ICB as shown by a prospective study assessing 40 individuals at baseline and 2 years later, whereby the authors did not report greater cognitive impairment or executive dysfunction in patients with ICBs when compared to PD-ICB (Siri et al., 2015).

1.2.4 Physiopathology

ICBs appear to be associated with abnormalities of dopaminergic transmission and two main phenomena have been implicated in the genesis of these behavioural problems: excessive dopamine release in the ventral striatum and excessive dopamine D3 receptor (D3R) stimulation.

The notion that ICBs are a consequence of excessive dopaminergic stimulation of the ventral striatum derives from knowledge about the normal functioning of

the dopaminergic reward system and observations from functional neuroimaging studies in drug addiction and PD+ICB. Under normal circumstances, there is tonic release of dopamine from the ventral tegmental area into the nucleus accumbens (NAc), in the ventral striatum. Changes in this tonic release occurs in response to stimuli, with rewarding activities resulting in an increase in dopamine release, and non-rewarding outcomes leading to a decrease. Dopaminergic connections between the ventral striatum and the orbitofrontal cortex are vital to the brain's valuation process and influence decision making, i.e. a positive outcome means that the action will be associated with a higher probability of reward in the future, and in negative outcomes the ventral striatum signals to the orbitofrontal cortex that the stimulus has a higher future probability of negative outcome (Damier, 2015) (figure 1 on page 27).

It has been postulated that in PD there is prominent loss of dopaminergic neurons in the dorsal striatum with relative preservation of the ventral striatum. The use of dopaminergic medication to treat PD symptoms could, therefore, overdose the ventral striatum and disrupt the decision making process, leading to the development of ICBs (Djamshidian et al., 2011b). This idea has been supported by functional neuroimaging studies. In PD patients with DDS, levodopa has been shown to induce excessive release of dopamine in the ventral striatum (Evans et al., 2006). The same finding has been reported in PD patients with other types of ICBs, including pathological gambling, CSB, compulsive shopping, compulsive eating and punding (O'Sullivan et al., 2011). Many authors have classified ICBs as behavioural addictions because similar phenomena have been observed in drug addiction. Functional neuroimaging has also been used to report greater decreases in binding potential in the ventral striatum of individuals with PD and pathological gambling, which could be a consequence of increased dopamine release or reduced D2R and D3R availability (Steeves et al., 2009). In PD patients with CSB the increased sexual desire and hedonic response has been correlated with activation of the ventral striatum, cingulate and orbitofrontal cortices (Politis et al., 2013).

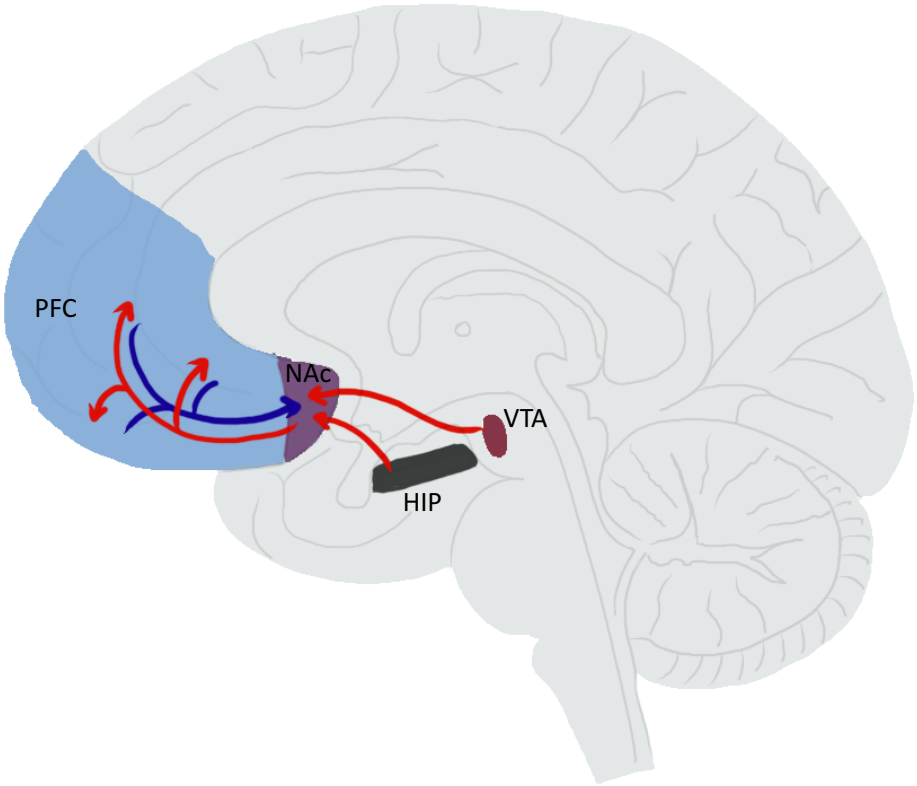


Figure 1. Important structures of the dopaminergic reward pathway.

There is tonic release of dopamine from the ventral tegmental area (VTA, in dark red) into the nucleus accumbens (NAc, in purple) that changes according to the rewarding nature of a stimulus. Increases in dopamine release as a consequence of rewarding stimuli will reduce the prefrontal cortex (PFC, in blue) input via D2 inhibitory pathways and increase the hippocampal subiculum input (in dark grey) through D1 excitatory connections. Non-rewarding stimuli results in a reduction in dopamine release, removing the input from the subiculum and reducing PFC inhibition, allowing attention to shift to a new stimulus.

Data from clinical observational studies showing that DA are the strongest risk factor for ICBs (Weintraub et al., 2010a) coupled with the fact that all DA are agonists of D3R is the basis to the theory that impulse control disorders in PD are a consequence of excessive D3R stimulation. In fact, most of the clinically available DA have higher affinity for D3R compared to D2R and the avidity with which a DA binds the D3R in comparison to the D2R has been correlated with increased risk of ICBs as displayed in figure 2 on page 29 (Seeman, 2015). Supporting this idea, stimulation of dopamine receptors by DA impair negative feedback signalling (van Eimeren et al., 2009) and PD+ICB using DA have a tendency to consider outcomes as “better than expected” (Voon et al., 2010).

Other functional abnormalities have also been associated with ICBs in PD, such as a defective inhibitory network and a functional disconnection between brain structures involved in reward processing (van Eimeren et al., 2010, Premi et al., 2016). Lower availability of the dopamine transporter in drug-naïve PD patients has been retrospectively associated with the development of IBCs (Vriend et al., 2014) but similar findings have also been reported in PD+ICB and could mean either downregulation of the transporter or a pre-existing trait (Cilia et al., 2010). Other neurotransmitters might also be implicated in ICBs according to a recent publication where the authors reported a significant association between tryptophan hydroxylase type 2 gene variant, the severity of addictive behaviours and lower remission rates in PD patients (Cilia et al., 2016).

Preliminary studies have suggested a role for genetic polymorphisms in the development of ICBs (table 2 on page 30). In healthy individuals, ropinirole can either increase or decrease impulsivity according to the expression of five genes: catechol-O-methyltransferase, dopamine transporter and genes encoding D1R, D2R and D3R (MacDonald et al., 2016). DRD1, DRD2 and GRIN2B gene variants have been associated with increased risk for ICBs in PD patients from Malaysia (Zainal Abidin et al., 2015). In Indian PD patients, one variant of the DRD3 gene has been positively correlated with ICBs (Krishnamoorthy et al., 2016). Variation in OPK1, HTR2A and DDC have also been reported to increase the risk for ICBs (Kraemmer et al., 2016). Genome-wide association studies involving larger number of participants are needed to confirm these findings.

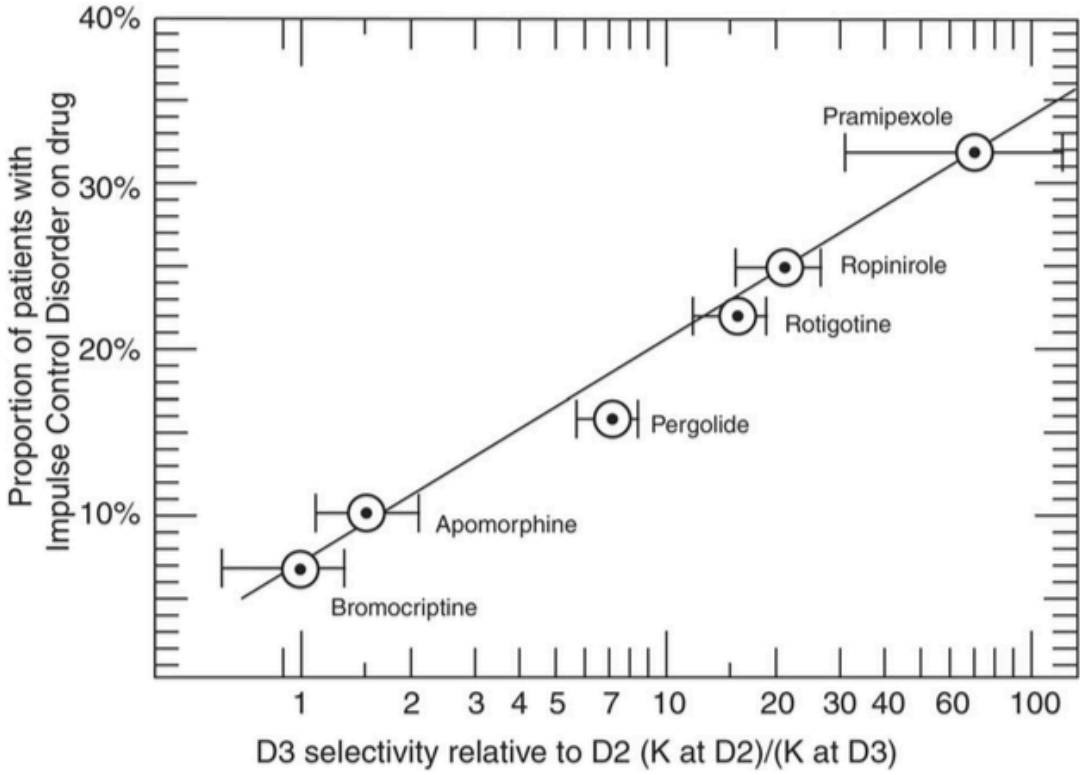


Figure 2. Dopamine D3 receptors and impulse control disorders.

The image shows the proportion of patients who develop impulse control disorders (y axis) when using dopamine agonists with different levels of affinity to dopamine D3 receptor relative to D2 (x axis). There is a direct correlation between the development of impulse control disorders and dopamine agonist selectivity of dopamine D3 receptors relative to D2. Reproduced with permission from ©Wiley Periodicals Inc (Seeman, 2015).

Table 2. Genetic polymorphisms studies of PD patients with ICBs

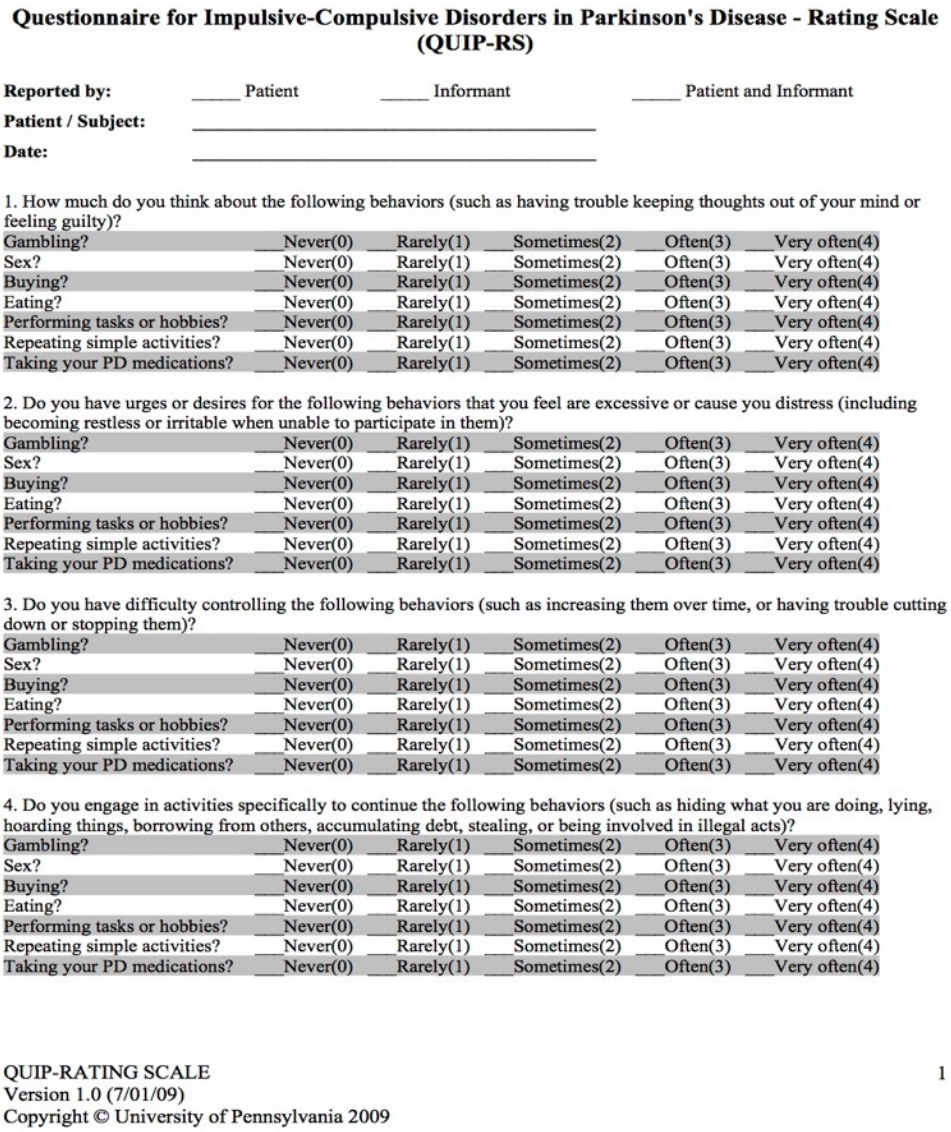
Study	Country	Participants	Genes	Results
Zainal Abdin et al, 2015	Malaysia	52 PD+ICB and 39 PD-ICB	DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2B	Variants of DRD1, DRD2 and GRIN2B associated with ICBs
Krishnamoorthy et al, 2016	India	70 PD+ICB, 100 PD-ICB and 285 healthy controls	DRD3, GRIN2B and HTR2A	DRD3 p.Ser9Gly variant associated with ICBs in PD
Kraemmer et al, 2016	International study	276 patients with PD, 19% reported ICB	DRD2, DRD3, DAT1, COMT, DDC, GRIN2B, ADRA2C, SERT, TPH2, HTR2A, OPRK1 and OPRM1	OPK1, HTR2A and DDC strongly associated with ICBs

Overview of previous studies investigating genetic polymorphisms in PD+ICB. PD+ICB – patients with Parkinson's disease and impulsive compulsive behaviours; PD-ICB – patients with Parkinson's disease without impulsive compulsive behaviours; DRD1 – dopamine D1 receptor; DRD2 – dopamine D2 receptor; DRD3 – dopamine D3 receptor; DRD4 – dopamine D4 receptor; DRD5 – dopamine D5 receptor; GRIN2B – N-methyl-D-aspartate 2B; HTR2A – serotonin receptor; COMT – catechol-O-methyltransferase; DAT – dopamine transporter; DDC – dopa decarboxylase; ADRA2C – adrenergic receptor; SERT – serotonin.

1.2.5 Diagnosis

PD patients have a tendency to under-report adverse events from medication, which is more evident with neuropsychiatric symptoms, such as ICBs (Perez-Lloret et al., 2012b). Additionally, lack of insight and deliberate concealment can further contribute to under-reporting of ICBs (Averbeck et al., 2014). This potentially leads to late diagnosis of behavioural addictions, bringing serious consequences to patients' lives, such as debt and deterioration of personal relationships. Timely and accurate detection of ICBs is vital to avoid such complications.

Although many screening instruments for ICBs have been developed, the most widely used is the QUIP (Weintraub et al., 2009). It is a sensitive instrument whether completed by the patient or carer with 100% negative predictive value, and a positive predictive value of approximately 37%. Agreement between patient and informant is higher for gambling and lower for buying, eating and CSB, which can be the result of lack of insight or that the latter behaviours are more likely to be concealed (Papay et al., 2011). Another version of the QUIP was developed subsequently, the QUIP-RS (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating scale) (figure 3 on page 32) which not only identifies ICBs but also measure their severity with good sensitivity and specificity values (Weintraub et al., 2012). However, relying solely on screening tools such as the QUIP to diagnose ICBs can result in a large number of false positives, meaning that the golden standard method for diagnosing ICBs is the clinical interview. Ideally the interview should include the patient's carer/spouse to reduce the possibility of under-reporting (Papay et al., 2011).



Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Reported by: _____ Patient _____ Informant _____ Patient and Informant

Patient / Subject: _____

Date: _____

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

QUIP-RATING SCALE 1
Version 1.0 (7/01/09)

Figure 3. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).

The QUIP-RS is a screening tool designed to detect and measure the severity of the following ICBs: pathological gambling, compulsive sexual behaviour, compulsive shopping, compulsive eating, punding/hobbyism and dopamine dysregulation syndrome. Four main questions assess how much each ICB interfere with patients' daily lives. The higher the total score, the more severe the behavioural addiction.

1.2.6 Treatment

Vigilance is required whenever a patient is started on DA. In the case of patients who have already developed ICBs, it is important to involve relatives, carer and general practitioner to provide adequate support and limit access to medication when needed, particularly in cases of DDS. It may also be necessary to limit access to finances in cases of compulsive shopping and pathological gambling. Poor or lacking caregiving/social support is associated with worse DDS outcome and relapses (Cilia et al., 2014).

The main treatment strategy for ICBs is the reduction of dopaminergic medication (Averbeck et al., 2014). In patients with DDS, reduction of dopaminergic therapy is the most effective treatment with greater success rates seen when reductions of more than 55% of levodopa compared to baseline are achieved (Cilia et al., 2014). In PD+ICB using DA, reduction and withdrawal of this drug is the treatment of choice, as corroborated by several observational studies (Bastiaens et al., 2013, Sohtaoglu et al., 2010, Mamikonyan et al., 2008, Macphee et al., 2009). When tapering a DA it is important to monitor patients for dopamine agonist withdrawal syndrome (DAWS), which causes distressing physical and psychological symptoms (Nirenberg, 2013). DAWS can affect 15 to 19% of individuals with PD on DA (Rabinak and Nirenberg, 2010, Pondal et al., 2013, Cunnington et al., 2012) and is defined by Rabinak and Nirenberg as ‘a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other PD medications, and cannot be accounted by other clinical factors’ (Rabinak and Nirenberg, 2010). Psychiatric symptoms such as depression, anxiety, agitation and dysphoria are common and can be accompanied by nausea, dizziness, generalised pain, diaphoresis and drug cravings. These symptoms do not respond to antidepressants, benzodiazepines or levodopa and usually subside when the DA is reinstated. Risk factors for DAWS are the presence of ICBs and higher daily dose of DA (Yu and Fernandez, 2017).

Cognitive behavioural therapy can be useful in the treatment of PD+ICB. Individuals with lower burden from ICBs, better social input and on lower doses of antiparkinsonian medication are the ones with the greater potential to derive benefit from this intervention (Okai et al., 2015).

A clinical trial of naltrexone involving 50 patients with PD and impulse control disorders failed to achieve its primary outcome measure, the clinician-rated global impression of change scale. However, there was a reduction in severity of symptoms leading the authors to conclude that further studies are needed (Papay et al., 2014). There are case reports of improvement of PD+ICB with diverse drugs: quetiapine in pathological gambling (Sevincok et al., 2007); clozapine for CSB with paraphilias (Fernandez and Durso, 1998) and pathological gambling (Rotondo et al., 2010); valproate for CSB, pathological gambling, walkabout behaviour and DDS (Hicks et al., 2011); carbamazepine for CSB (Bach et al., 2009); topiramate for CSB, pathological gambling, compulsive shopping and compulsive eating (Bermejo, 2008); zonisamide for CSB, pathological gambling, compulsive shopping and compulsive eating (Bermejo et al., 2010); finasteride for pathological gambling (Bortolato et al., 2012); naltrexone for pathological gambling (Bosco et al., 2012); donepezil for CSB (Ivanco and Bohnen, 2005); and amantadine for pathological gambling (Thomas et al., 2010). Amantadine has also been assessed in larger studies with contradictory results. Whilst a randomized crossover study involving 17 PD patients with pathological gambling refractory to reduction or cessation of DA showed resolution of the abnormal behaviour in 7 (Thomas et al., 2010), a retrospective analysis of the DOMINION study cohort showed that the use of amantadine was associated with impulse control disorders (Weintraub et al., 2010b). Psychiatric complications of DDS such as psychosis and aggressive behaviour can be managed with clozapine (Cilia et al., 2014).

Preliminary data available on infusion therapies for PD, apomorphine and levodopa intestinal gel, suggests a lower risk profile for triggering ICBs (Martinez-Martin et al., 2014, Todorova, 2013), with the exception of one study involving 15 patients on levodopa-carbidopa intestinal gel that reported 4 *de novo* cases of ICBs (Chang et al., 2016).

Deep brain stimulation (DBS) is a highly effective treatment for PD with evidence supporting its use in individuals with young onset PD and early in the course of the disease (Schuepbach et al., 2013). Several studies have addressed its safety in PD+ICB generating contradictory data. One study assessed 56 patients receiving DBS of the subthalamic nucleus (STN) for up to 3 years. Thirteen patients had ICBs before surgery and, three years after, 11 of them had fully remitted and the remaining two improved partially. However, this effect can be explained by concomitant reduction of DA dose. Six patients developed new onset ICBs after surgery with spontaneous recovery afterwards (Amami et al., 2015). Ardouin and colleagues followed up 7 patients with pathological gambling after DBS of the STN. All cases resolved after an average period of 18 months concomitant with reduction of 74% of the dopaminergic treatment (Ardouin et al., 2006). One-hundred and fifty PD patients with STN DBS were assessed for pre and post-surgical prevalence of ICBs. The authors found that two thirds of the patients experienced remission with chronic DBS, with significant improvement in CSB, gambling and DDS. Eleven patients developed new-onset ICBs (Merola et al., 2016). A meta-analysis showed that 27 studies with different methodologies addressed the risk profile of DBS for ICBs. Out of 226 patients reviewed, 88 *de novo* cases were reported, 138 had ICBs before surgery. One-hundred and thirty underwent bilateral STN DBS with 79% of the patients improving. Among these, *de novo* ICBs were reported in 15.11% (Kasemsuk et al., 2017). There is not enough data on the literature to assess if stimulation of the pallidus is safer than stimulation of the STN. Improvement of ICBs seen in some patients after STN DBS is likely a consequence of concomitant reduction of dopamine replacement therapy. A definitive answer to this questions could be provided by future prospective studies (Okun and Weintraub, 2013).

1.2.7 Prognosis

Limited data is available on the long-term prognosis of ICBs. Cross-sectional and prospective studies have been published with the longest of them covering a period of four years. In common, these studies report that more than two thirds of patients improve and improvement is dependent on a significant reduction of DA dose (Mamikonyan et al., 2008, Sohtaoglu et al., 2010,

Bastiaens et al., 2013). However, QUIP scores may remain high even after improvement (Ramirez Gomez et al., 2017) and a significant proportion of patients fail to achieve remission.

1.3 Aims of this thesis

In chapter 2 the long-term prognosis of ICBs is examined. A population of PD+ICB was re-assessed after approximately 8 years of follow up. Data on remission rate, treatment strategies, neuropsychiatric and clinical features is provided.

Chapter 3 describes clinical studies that have focused in specific types of ICBs. CSB was compared to other types of ICBs and its association with clinical and neuropsychiatric features and dopaminergic treatment investigated. The outcome of DDS until death was assessed in a population of patients who donated their brains for research. The clinical and neuropsychiatric features of punding were assessed in comparison to PD-ICB. The propensity of apomorphine continuous infusion to trigger ICBs was analysed in a population of individuals with advanced PD.

Automatic and voluntary saccadic eye movements of PD+ICB were investigated for the first time in chapter 4. Results were compared to PD-ICB and healthy controls. Data on saccadic metrics obtained from both pro-saccades and anti-saccades tasks are revealed as well as participant's ability to suppress automatic saccades, measured by the proportion of anti-saccadic direction errors.

Chapter 5 describes the first post mortem study of individuals with PD and DDS. Using immunohistochemistry techniques, the amount of alpha-synuclein pathology and tyrosine hydroxylase staining was assessed in the NAc, dorsal putamen and dorsal caudate of individuals with ICBs and compared to individuals who had PD but did not report ICBs in life. The levels of D2R and D3R in the NAc, putamen and frontal cortex were also compared using western immunoblotting.

Chapter 2: The long-term outcome of impulsive compulsive behaviours in Parkinson's disease

2.1 Introduction

The main risk factors for developing ICBs are a younger age of PD onset, male sex and dopaminergic treatment, particularly DA (Weintraub et al., 2010a). Whilst 1 in 7 patients with PD will develop these behavioural abnormalities, the 5-year cumulative incidence of ICBs was reported to be 46.1% in a recent longitudinal study (Corvol et al., 2018). Furthermore, up to 39% of PD patients on therapeutic doses of DA develop ICBs after 6 months of treatment (Garcia-Ruiz et al., 2014).

Few studies have assessed the outcome of ICBs. In one of them, 10 out of 15 patients interviewed by phone after 29 months were completely free of ICBs (Mamikonyan et al., 2008). In another study, 22 patients were reassessed after 43 months and only six were considered by their families and doctors to still have troublesome ICBs (Sohtaoglu et al., 2010). In both cases a significant proportion of patients successfully stopped or markedly reduced the dose of DA. In a prospective non-interventional study, 1069 PD patients were followed up for two years revealing that approximately one third had developed ICBs. The prevalence of behavioural addictions remained stable throughout the study period (Antonini et al., 2017).

Longitudinal data on a large group of PD+ICB who were followed up for a mean period of 8.2 years is presented here, representing the largest and longest follow up study to date. Motor symptoms, neuropsychiatric complications, cognitive status, quality of life, dopaminergic treatment and outcome of ICBs were assessed.

2.2 Materials and methods

2.2.1 Study design and patient selection

PD+ICB who participated in previous studies (visit 1 – V1) at the National Hospital for Neurology and Neurosurgery, Queen Square, London, from 2007 to 2012 were invited to attend a new assessment between 2016 and 2017 (visit 2 – V2). All patients had received a diagnosis of ICBs during an interview conducted by a movement disorders specialist. At V1, participants were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part III and an interview to collect clinical and treatment data, focusing on ICBs, cognition, dopaminergic treatment, motor and neuropsychiatric symptoms.

The study received approval by the Queen Square Ethics Committee and all patients gave informed consent. A few days before V2, patients received the following self-assessment questionnaires via post: The QUIP-RS, the Hospital Anxiety and Depression Scale (HADS) and the 36-Item Short Form Survey (SF36). Subsequently, patients were assessed during a hospital visit or at home (V2), if they were unable to make the journey to the hospital. During this assessment, demographic and clinical data were collected and the following scales/questionnaires used: the UPDRS parts I and III during ON period, the Abnormal Involuntary Movement Scale (AIMS), the Frontal Assessment Battery (FAB) and the Montreal Cognitive Assessment (MoCA).

The diagnosis of ICBs at V2 was made based on the QUIP-RS scores using previously published cut-off values (Weintraub et al., 2009) and confirmed with a structured interview, conducted with the patient and spouse/carer when available. The interview contained questions that addressed each diagnostic criteria for impulse control disorders from the Diagnostic and Statistical Manual of Mental Disorders IV. Since specific diagnostic criteria for dopamine dysregulation syndrome and punding are not available in the DSM-IV, proposed criteria from Giovannini et al (Giovannoni et al., 2000) and O'Sullivan et al (O'Sullivan et al., 2007) were also included in the interview. When the results of the QUIP-RS and the interview were discordant, the definitive diagnosis of ICBs was based on the interview.

2.2.2 Statistical analysis

Anonymised data was imported to SPSS 22 for statistical analysis. All variables were tested for normality and the appropriate statistical tests chosen accordingly. Parametric data was analysed using independent samples t-test and paired samples t-test. Non-parametric data was analysed using Mann-Whitney U test and Wilcoxon matched pairs. Proportions were compared with the McNemar's test and Pearson chi-square test; the latter was replaced with the Fisher's exact test if the minimum expected cell count was less than five. A p value of less than 0.05 was considered significant, except for comparison between visits, when Bonferroni correction was applied and significance was reached when the p value was less than 0.025.

2.3 Results

2.3.1 Recruitment

Ninety individuals who were assessed at V1 were identified. Among these, 46 were included in this study. Eight declined to participate, five were lost to follow up and 31 had died (figure 4 on page 40). Death certificates were available for 26 patients. Respiratory conditions were the most common cause of death (13 patients – 11 pneumonia and 2 pulmonary embolism), followed by PD (5 deaths) and cancer (3 cases). Cardiac arrhythmia, old age, sepsis, stroke and gastro-intestinal bleed were the cause of death in one case each. No cases of suicide or traumatic fatality were reported.

2.3.2 Demographic and clinical data of the entire cohort

The study population consisted mostly of males with early onset PD and mean disease duration of 17 years. Mean follow up duration was just over 8 years. Three patients had been diagnosed with a genetic form of PD, all three carrying a bi-allelic PARKIN mutation. At V2, 3 patients were in residential care, and 4 on atypical neuroleptic drugs. Deceased patients were older at disease onset and had longer disease duration (table 3 on page 41).

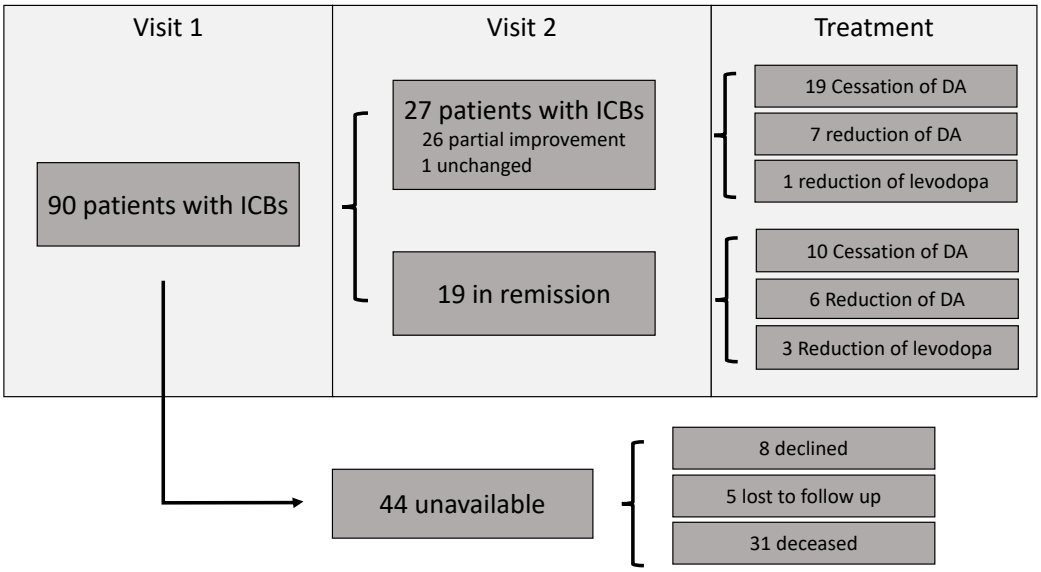


Figure 4. The outcome of impulsive compulsive behaviours (ICBs) according to treatment strategies.

Ninety patients were assessed at visit 1 and 46 were available for visit 2. Whilst 27 patients were still being troubled by ICBs, 19 had experienced complete remission. The most used treatment strategies in both groups were: cessation of DA, reduction of DA and reduction of levodopa. 44 patients were unavailable for reassessment: 8 declined participation, 5 were lost to follow up and 31 had died.

Table 3. Demographic and clinical data of the entire cohort

	N = 46	Deceased (N = 31)	p value
Male sex	37 (80.4%)	25 (80.6%)	0.982φ
Age at PD onset (years)	45.1 (± 9.6)	50.38 (± 10)	**0.025***
Disease duration (years)	17 (± 7.9)	20 (± 7.1)	**0.036****
Follow up duration (months)	98.3 (± 31.8)		
Genetic PD	3 (6.5%)		
In residential care	3 (6.5%)		
On neuroleptic drugs	4 (8.7%)		

*Demographic and clinical data of the entire cohort. Demographic data from deceased patients was also included. Forty-six patients who were followed up for 8.2 years were available for reassessment. PD – Parkinson's disease. Results expressed in total values and proportions or means and standard deviation. φchi-square test; *t-test for independent samples; **Mann-Whitney U test. Significant results in bold.*

2.3.3 Comparison between visit 1 and visit V2

Participants' average age was 54.7 years at V1 and 61.7 at V2. All 46 patients had received a diagnosis of ICBs at V1, among these 58.7% had multiple ICBs. At V2 more than half of the patients were still being troubled by ICBs, nearly 60% of them had multiple ICBs. Details on the types of ICBs at each visit can be seen in table 4 on page 43.

Apomorphine was considered separately from other DA in all comparisons. This decision was based on the different pharmacological profile of apomorphine compared to other DA. Initial treatment of ICBs consisted of cessation of oral/transcutaneous DA in 29 patients, reduction of DA dose in 13 and reduction of levodopa in 4. Among the patients who stopped or reduced oral/transcutaneous DA, seven (16.6%) developed DAWS. Of the 46 patients, 19 improved completely and were asymptomatic at V2, 26 improved partially and 1 had no change of the addictive behaviour. None of the patients experienced worsening of ICBs over time. Five patients re-started oral/transcutaneous DA during disease course. Details on the outcome of ICBs according to treatment can be seen in figure 4.

Average UPDRS part III scores and the prevalence of levodopa-induced dyskinesias increased significantly between the two assessments (table 4). The cognitive status of all 46 patients at V1 was available: four had been diagnosed with mild cognitive impairment, 2 had significant cognitive impairment and 40 were cognitively intact. At V2, cognition was tested with the MoCA revealing that 32% of the patients scored below cut-off values and were considered to have cognitive impairment. There were no statistically significant differences on the prevalence of anxiety, depression and visual hallucinations between visits (table 4).

Only five patients were not using levodopa at V1 and only two at V2. More participants were using MAOi and amantadine at V2. Total levodopa daily dose and total dopaminergic treatment dose measured in levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010) were significantly higher at V2 (table 4).

Table 4. Comparison between visits			
	Visit 1 (V1)	Visit 2 (V2)	p value
Age (years)	54.7 (± 9.7)	61.7 (±10.2)	**<0.001***
ICBs	46 (100%)	27 (58.7%)	**<0.001λ**
Multiple ICBs	27 (58.7%)	16 (59.2%)	0.754λ
DDS	6	3	0.508λ
CSB	23	13	0.052λ
Pathological gambling	13	5	**0.008λ**
Compulsive shopping	17	5	**0.008λ**
Compulsive eating	11	14	0.629λ
Punding	23	18	0.359λ
UPDRS III	16.2 (± 7.8)	34.65 (± 11)	**<0.001***
Dyskinesias	29 (63%)	38 (82.6%)	**0.022λ**
Cognitive impairment	2 (4.3%)	15 (32.6%)	**0.001λ**
Depression	14 (30.4%)	11 (23.9%)	0.629λ
Anxiety	8 (17.4%)	15 (32.6%)	0.118λ
Hallucinations	10 (21.7%)	12 (26.1%)	0.754λ
Levodopa use	41 (89.1%)	44 (95.6%)	0.375λ
DA use	42 (91.3%)	18 (39.1%)	**<0.001λ**
MAOi use	8 (17.4%)	28 (60.9%)	**<0.001λ**
Amantadine use	16 (34.8%)	37 (80.4%)	**<0.001λ**
Levodopa dose	713.7 (± 487) N=41	1021 (± 437) N=44	**0.001φ**
DA LEDD	255.6 (± 113) N=42	153.4 (± 86.9) N=18	**0.003φ**
Total LEDD	979.6 (± 542.8)	1296.6 (± 457.7)	**<0.001φ**
Infusion therapies	Apomorphine: 2.1%	Apomorphine: 6.5% Duodopa: 2.1%	
Deep brain stimulation	0	11 (23.9%)	

*Comparison between visits. ICBs – impulsive compulsive behaviours; DDS – dopamine dysregulation syndrome; CSB – compulsive sexual behaviour; UPDRS – Unified Parkinson's Disease Rating Scale; DA – oral/transcutaneous dopamine agonists; MAOi – monoamine oxidase inhibitor; LEDD – levodopa equivalent daily dose. Results expressed in total values and proportions, or mean values and standard deviation. A p value of less than 0.025 was considered significant (in bold) after Bonferroni correction. *paired t-test; φ Wilcoxon matched pairs; λ McNemar's test.*

At V1, 42 patients were using oral/transcutaneous DA: 27 pramipexole, 12 ropinirole, 1 rotigotine, 1 bromocriptine and 1 cabergoline. Eighteen patients were using DA at V2: 8 were using pramipexole, 3 ropinirole and 7 rotigotine. There was a significant reduction of oral/transcutaneous DA use at V2. Regarding advanced therapies, 1 patient was using apomorphine infusion at V1; at V2 3 patients were using apomorphine infusion and 1 duodopa intestinal gel. Eleven participants underwent DBS, 10 of the subthalamic nucleus and 1 of the globus pallidus (table 4).

Additional scales and questionnaires were used at V2 to assess severity of ICBs, neuropsychiatric complications, quality of life, severity of PD, involuntary movements and cognitive status. Results can be seen in table 5 on page 45.

2.3.4 Comparison between patients who experienced remission and patients with persistent ICBs

Participants were divided into two groups based on the presence of ICBs at V2: PD patients with active ICBs (PD+V2ICB) and patients who experienced complete remission of ICBs (PD-V2ICB); and compared to identify any factors associated with long-term remission as detailed in table 6 on page 46. There were no differences in clinical and demographic data, marriage status and duration of follow up. Oral/transcutaneous DA LEDD and levodopa daily dose, as well as peak DA dose did not differ between groups. PD+V2ICB patients used DA for longer and were on higher total LEDD but the difference did not reach significance.

The scores on the QUIP-RS, HADS total, HADS depression and UPDRS part I were higher on the PD+V2ICB group. Results of the other scales/questionnaires did not differ. Although patients with ICBs did not have higher burden of motor symptoms on the UPDRS III, Hoehn & Yahr results were different with more patients with advanced disease on the PD+V2ICB group.

Table 5. Results of the scales/questionnaires used at visit 2	
	N = 46
QUIP-RS	33.7 (± 19.2; 4 – 78)
HADS depression	8 (± 3.5; 1 – 16)
HADS anxiety	8.9 (± 4.2; 2 – 20)
HADS total	16.5 (± 6.7; 3 – 35)
SF36 general health	33.9 (± 17.9; 5 – 80)
SF36 physical functioning	35.1 (± 28; 0 – 95)
SF36 role limitations due to physical health problems	10.3 (± 23.9; 0 – 100)
SF36 role limitations due to personal or emotional problems	40.5 (± 40.3; 0 – 100)
SF36 energy/fatigue	36.8 (± 15.5; 10 – 65)
SF36 emotional well being	58.5 (± 19.3; 2 – 92)
SF36 social functioning	40.2 (± 25.6; 0 – 100)
SF36 bodily pain	47.6 (± 30.6; 0 – 100)
AIMS	7.8 (± 7.3; 0 – 24)
UPDRS I	19.5 (± 8.3; 6 – 41)
UPDRS III	34.6 (± 11; 12 – 61)
Hoehn & Yahr	2: 52.1%
	3: 34.8%
	4: 13.1%
FAB	15.2 (± 2.8; 6 – 18);
MoCA	25.5 (± 4.8; 7 – 30);

Results at visit 2. QUIP-RS – Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale; HADS – the Hospital Anxiety and Depression Scale; SF36 – the 36-Item Short Form Survey; UPDRS – Unified Parkinson's Disease Rating Scale; AIMS – Abnormal Involuntary Movement Scale; FAB – the Frontal Assessment Battery; MoCA – the Montreal Cognitive Assessment. Results expressed in mean values with standard deviation and range, and proportions for the Hoehn & Yahr scale.

Table 6. Comparison between patients with and without ICBs at V2			
	PD-V2ICB (N = 19)	PD+V2ICB (N = 27)	p value
Male sex	15 (78.9%)	22 (81.4%)	1.000†
Married	12 (63.1%)	18 (66.6%)	0.806φ
Age	61.1 (± 10.4)	62 (± 10.2)	0.769*
Age at PD onset	45.9 (± 8.9)	44.6 (± 10.2)	0.644*
Disease duration	15.2 (± 5.4)	18.2 (± 9.1)	0.214*
Months of DA use	70.3 (± 41)	89.7 (± 47.5)	0.157*
DA use (V1)	16 (84.2%)	26 (96.2%)	0.292†
DA use (V2)	7 (36.8%)	11 (40.7%)	0.790φ
DA LEDD (V1)	227.1 (± 97.6)	273.1 (± 120)	0.205*
	N = 16	N = 26	
DA LEDD (V2)	135.4 (± 69.9)	164.9 (± 97.6)	0.500*
	N = 7	N = 11	
Peak DA dose	312.8 (± 104)	311.6 (± 139)	0.468**
	N = 17	N = 27	
Levodopa use (V1)	17 (89.4%)	24 (88.8%)	0.950†
Levodopa use (V2)	18 (94.7%)	26 (96.3%)	1.000†
Levodopa daily dose (V1)	622.6 (± 302) N = 17	778.3 (± 582) N = 24	0.320*
Levodopa daily dose (V2)	959.8 (± 450) N = 18	1064.9 (±432) N = 26	0.440*
Total LEDD (V1)	907 (± 436.1)	1030.7 (± 609.7)	0.453*
Total LEDD (V2)	1197.6 (± 438.5)	1366.2 (± 496.4)	0.241*
MAOi (V2)	11 (68.7%)	17 (62.9%)	0.729φ
Amantadine (V2)	15 (78.9%)	22 (81.4%)	1.000†
Dyskinesias	16 (84.2%)	22 (81.4%)	1.000†
DBS	4 (21%)	7 (25.9%)	1.000†
QUIP-RS	23.3 (± 16.8)	41 (± 17.5)	**0.001***
HADS depression	6.7 (± 3.3)	9 (± 3.3)	**0.029***
HADS anxiety	7.7 (± 4.1)	9.7 (± 4.1)	0.117*
HADS total	14 (± 5.4)	18.4 (± 7)	**0.026***
AIMS	6.7 (± 6.9)	8.7 (± 7.6)	0.378*
UPDRS I	15. (± 6)	22.3 (± 8.7)	**0.003***

	PD-V2ICB (N = 19)	PD+V2ICB (N = 27)	p value
UPDRS III	33.5 (± 10.4)	35.4 (± 11.5)	0.567*
Hoehn & Yahr	2: 73.7%	2: 37%	**0.021**ᵠ
	3: 26.3%	3: 40.7%	
	4: 0%	4: 22.3%	
FAB	15.5 (± 2.7)	14.9 (± 2.9)	0.448*
MoCA	26.3 (± 3.3)	24.9 (± 5.6)	0.324*

*Comparison between patients with active ICBs (PD+V2ICB) and patients who improved completely (PD-V2ICB) at visit 2 (V2). V1 – Visit 1; PD – Parkinson's disease; DA – oral or transcutaneous dopamine agonists; LEDD – levodopa equivalent daily dose; MAOi – monoamine oxidase inhibitors; DBS – deep brain stimulation; QUIP-RS – Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale; HADS – the Hospital Anxiety and Depression Scale; SF36 – the 36-Item Short Form Survey; UPDRS – Unified Parkinson's Disease Rating Scale; AIMS – Abnormal Involuntary Movement Scale; FAB – the Frontal Assessment Battery; MoCA – the Montreal Cognitive Assessment. Results expressed in total values and proportion, or mean values and standard deviation. Significant results in bold. †Fisher's exact test; *independent samples t-test; ᵠ chi-square; **Mann-Whitney U test.*

To investigate whether different types of ICBs were associated with different dopaminergic drugs, patients were again sub-divided into two groups, but this time based on the type of ICB present at V1: patients with DDS and/or punding (PD+V1DDS/pu) and PD patients with other ICBs (PD-V1DDS/pu). Statistical analysis showed that there were no significant differences in any of the variables tested as seen in table 7 on page 49. Further comparison between PD+V1DDS/pu and PD-V1DDS/pu according to remission status also failed to reveal significant differences. PD+V1DDS/pu, who were no longer actively demonstrating addictive behaviours at V2, still had a 40% increase in levodopa intake during the interval (607mg up to 1046mg/day). This compared to an approximately 25% increase in levodopa intake amongst patients with persistent DDS/punding behaviours at V2 (886mg up to 1102mg/day) (table 7).

Table 7. Comparison between patients with DDS/punding and other ICBs

	PD+V1DDS/pu (N = 26)	PD-V1DDS/pu (N = 20)	p value
Male sex	22 (84.6%)	15 (75%)	0.472†
Age	61.7 (± 9.9)	61.6 (± 10.8)	0.956*
Age at PD onset	44.7 (± 9.4)	45.6 (± 10.1)	0.763*
DA use (V1)	23 (88.4%)	19 (95%)	0.622†
DA use (V2)	13 (50 %)	8 (40%)	0.500ᵠ
DA LEDD (V1)	264.6 (± 97.3) N = 23	244.6 (± 131.5) N = 19	0.574*
DA LEDD (V2)	143.8 (± 93) N = 11	168.5 (± 79.6) N = 7	0.572*
Peak DA dose	295.3 (± 102) N = 24	332.2 (± 149) N= 20	0.493**
Levodopa use (V1)	22 (84.6%)	19 (95%)	0.369†
Levodopa use (V2)	24 (92.3%)	20 (100%)	0.498†
Levodopa daily dose (V1)	797.1 (± 526.5) N = 22	617.2 (± 431.2) N = 19	0.243*
Levodopa daily dose (V2)	1085.8 (± 461.1) N = 24	945.1 (± 405.5) N = 20	0.294*
Total LEDD (V1)	1018.8 (± 599.2)	928.7 (± 469.6)	0.583*
Total LEDD (V2)	1329.5 (± 488.1)	1253.7 (± 468.2)	0.598*
iMAO (V2)	14 (53.8%)	14 (70%)	0.266ᵠ
Amantadine (V2)	21 (80.7%)	16 (80%)	1.000†

*Comparison between patients with DDS and/or punding (PD+V1DDS/pu) and patients with other ICBs (PD-V1DDS/pu) at visit 1. PD – Parkinson's disease; ICBs – impulsive compulsive behaviours; DDS – dopamine dysregulation syndrome; DA – oral or transcutaneous dopamine agonists; LEDD – levodopa equivalent daily dose; MAOi – monoamine oxidase inhibitors; Results expressed in total values with proportion, or mean values with standard deviation and range. Significant results in bold. †Fisher's exact test; *independent samples t-test; ᵠchi-square; **Mann-Whitney U test.*

2.4 Discussion

The long-term outcome of ICBs in a large cohort of patients with PD is presented in this chapter, the longest follow up study of PD+ICB to date. Analysis offers new insights into treatment strategies, associated clinical features and prognosis of this disabling condition.

The treatment of choice for ICBs is reduction of dopaminergic treatment (Mestre et al., 2013). The literature shows that, in DDS, greater remission rates are seen among patients who have managed to achieve higher reduction in dopaminergic treatment dose (Cilia et al., 2014). In this study, all but one patient improved after reduction of PD treatment, confirming the strong association between ICBs and dopaminergic medication (Weintraub et al., 2010a).

In patients using DA, ICBs commonly improve after reduction or removal of the drug (Evans et al., 2009, Bastiaens et al., 2013). In line with this, previous reports on the outcome of ICBs found that remission is associated with reduction or discontinuation of DA. A retrospective study assessed 15 patients with PD and pathological gambling that experienced complete remission of the abnormal behaviour 21 months after cessation of DA (Macphee et al., 2009). In another study 15 PD+ICB were assessed by telephone after 29.2 months. Twelve participants either discontinued or significantly decreased DA and ten participants no longer met diagnostic criteria for ICBs (Mamikonyan et al., 2008), however there is a possibility of under-reporting of ICBs associated with the telephone assessment (Mamikonyan et al., 2008). Sohtaoglu and collaborators reported on 22 PD+ICB after 43.2 months. Sixteen patients were free of addictive behaviours after a significant reduction in DA dose (Sohtaoglu et al., 2010). Finally, a recently published longitudinal study designed to assess the influence of DA in the development of impulse control disorders found a 50% remission rate in patients who completely stopped DA (Corvol et al., 2018).

The remission rate of ICBs reported here was lower than that reported by the aforementioned studies (Mamikonyan et al., 2008, Sohtaoglu et al., 2010), despite a similar proportion of patients using DA at V2 and a significant

reduction in DA dose between visits. Continued use of DA by a significant proportion of the patients is a possible explanation for the lower remission rate. DAWS prevented reduction of oral/transcutaneous DA in at least seven patients, a similar proportion to previously reported figures (Rabinak and Nirenberg, 2010). Undocumented DAWS may have been a factor in why other patients remained on DA, but this may not have been elaborated on by patients who (anecdotally) may simply describe “feeling better on the DA”. Another possibility is that following initial reduction of dopaminergic treatment and improvement, some patients may have experienced relapse of ICBs after additional increases in treatment required for disease progression as levodopa has also been associated with ICBs (Weintraub et al., 2010a). This is supported by the increase in total LEDD seen at V2 and the fact that 5 patients resumed use of DA later in the disease course. Finally, it is possible that the lower remission rate found is a consequence of the inclusion of more severe cases at V1 compared to other studies as a structured interview has greater sensitivity than the QUIP-RS for detection of clinically relevant ICBs, and all patients were seen at a tertiary centre (Papay et al., 2011).

Although ICBs have been associated with DA use in a dose-dependent fashion in a longitudinal study (Corvol et al., 2018), according to our results neither duration of DA use, peak DA dose, DA dose at V1 and DA dose at V2 influenced the long-term remission of ICBs. This was also true after patients were compared according to the presence of DDS/punding. This is compatible with other studies showing similar dose of levodopa, DA and total dopaminergic treatment between PD+V2ICB and PD-V2ICB at follow up (Sohtaoglu et al., 2010, Siri et al., 2015). Long term ICB remission appears to be associated with diverse factors. It has been postulated that drug addiction is perpetuated by brain plasticity that forms long-lasting maladaptive changes (Dong and Nestler, 2014). Considering the shared pathophysiological mechanisms between drug addiction and ICBs (O'Sullivan et al., 2011), it is possible that similar changes are contributing to the low long-term remission of ICBs.

DDS and punding are more commonly associated with drugs that preferentially stimulate dopamine receptors D1 and D2, such as levodopa (Katzenschlager, 2011, Fasano and Petrovic, 2010), whereas other ICBs are more commonly

seen with oral/transcutaneous DA use (Weintraub et al., 2010a). The comparison between patients with DDS/punding and other ICBs did not reveal any association with specific types of dopaminergic medication. One possible explanation is that patients were seen after diagnosis when initial reduction of dopaminergic treatment had already started. The outcome of DDS/punding was also not influenced by dopaminergic treatment at V2, similar to the analysis grouping all ICBs together.

A higher prevalence of multiple ICBs than previously reported was found (Antonini et al., 2017, Weintraub et al., 2010a, Garcia-Ruiz et al., 2014). Selection bias towards more severe cases is a possible explanation as previously explained. Despite more than 40% of the patients experiencing remission and nearly all of the remaining cases showing reduction in ICB severity, the proportion of patients having multiple ICBs remained stable at V2, in line with the literature. One prospective study assessed the prevalence of ICBs over a two-year period and found that the proportion of patients with multiple ICBs assessed by the QUIP (45%) remained stable over time (Antonini et al., 2017).

Compared to V1, fewer patients were using DA and more patients were using MAOi and amantadine at V2. This likely reflects the clinical practice of using MAOi to compensate for motor deterioration after the reduction in DA. The increase in amantadine use is likely an attempt to control levodopa induced dyskinesias, a common comorbidity of PD+ICB (Voon et al., 2009). Although both these classes of drugs appear to be safer than DA in patients with ICBs, contradictory data has been published on the propensity of amantadine to induce ICBs and case reports of ICBs on patients with MAOi have been published (Averbeck et al., 2014).

More patients were using rotigotine and apomorphine at V2. Some studies have reported a lower proclivity of both these drugs to induce ICBs (Antonini et al., 2016, Magennis, 2012, Todorova et al., 2013), possibly because of reduced D3R stimulation (Seeman, 2015) and, in the case of apomorphine, less reinforcing properties associated with continuous infusion as drugs that

stimulate faster clearance and re-uptake of dopamine (pulsatile stimulation) have more reinforcing properties (Volkow et al., 2004).

The risk of dementia in PD increases with age and disease duration. Nineteen percent of PD patients with an average age at disease onset of 34 develop cognitive impairment after 18 years of disease progression (Schrag et al., 1998). Whereas in PD patients with later disease onset (mean age 67) the prevalence of dementia after 10 years of disease is 46%. In the present study, a third of patients exhibited cognitive impairment at V2, suggesting that ICBs do not increase to any significant degree the risk for PD dementia, in line with a previous study that assessed the cognitive outcome in 40 PD+ICB after two years. The authors did not find greater cognitive impairment or executive dysfunction in PD+ICB when compared to PD-ICB (Siri et al., 2015).

Prevalence of depression at V1 was higher compared to published data from PD-ICB (Reijnders et al., 2008) confirming previous reports that PD+ICB are more likely to suffer from depression (Phu et al., 2014). Corroborating this association, the HADS depression scores were higher among PD+V2ICB. Quality of life measured by the SF36 was lower than the normative values published for patients with PD (Banks and Martin, 2009), particularly the general health, physical functioning, role limitations due to physical health and social functioning subscales, confirming previous data that ICBs are associated with worse quality of life (Phu et al., 2014).

Dyskinesias can affect up to 60% of PD patients after 10 years of disease progression (Van Gerpen et al., 2006), in line with our findings at V1. However, this was lower than the figure at V2, after approximately 17 years of disease progression. Younger age at PD onset, longer disease duration and longer exposure to levodopa are risk factors for the development of dyskinesias and could explain the higher prevalence at V2 (Zesiewicz et al., 2007).

A lower proportion of patients were using neuroleptic drugs at V2 compared with the results reported by Sohtaoglu and colleagues (Sohtaoglu et al., 2010). In their study, neuroleptics were used routinely if patients did not improve after initial treatment with reduction of DA, which was not our practice. However, the

fact that data from deceased patients was not available may have contributed to the exclusion of patients with more advanced disease and more likely to be using neuroleptic drugs.

Approximately one quarter of the patients underwent DBS. The literature suggests that DBS is safe in patients with previous ICBs, although a transient increase in impulsivity can occur after surgery (Amami et al., 2015). In the present study, seven patients were still symptomatic after DBS, but none experienced worsening of ICBs. The reduction in dopaminergic treatment that usually follows the procedure is a possible explanation for the low risk profile associated with DBS (Ardouin et al., 2006).

The comparison between PD-V2ICB and PD+V2ICB, showed that the latter scored higher on the UPDRS part I. The higher severity of NMS could explain this finding and has been reported before (Antonini et al., 2017). A higher proportion of patients with more advanced disease was also seen among PD+V2ICB patients. This contradicts other findings that ICBs are not associated with disease severity (Antonini et al., 2017, Antonini et al., 2011). One possible explanation is that patients with more advanced disease require higher doses of dopaminergic treatment and are, therefore, at increased risk of recurrence of ICBs.

Increased carer burden has been associated with behavioural abnormalities in PD (Leroi et al., 2012a) but it is unclear whether ICBs could lead to a higher divorce rate. The unchanged proportion of married individuals between PD+V2ICB and PD-V2ICB coupled with published data showing a similar number of married individuals in PD with and without ICBs (Leroi et al., 2012a) suggest that ICBs do not increase divorce rate in PD. However, larger studies are needed to answer this question.

One limitation of this study is that only half of the patients were available for re-assessment. The main reason for this is that approximately one third of the initial cohort had died at the time of reassessment. Although the mortality rate found here was lower than in a PD population after 10 years of disease progression (Williams-Gray et al., 2013), it is similar to what has been described

among patients with disease onset between the ages of 50 and 54 (Ishihara et al., 2007). Data currently being prepared by our group for publication on patients with PD without ICBs from the Queen Square Brain Bank shows a disease duration of 21.5 years when onset of the disease is around the age of 51, similar to the disease duration of the deceased group from this cohort. This suggests that patients with ICBs do not have a more aggressive phenotype of PD. However, it is important to acknowledge that ICBs are more prevalent in individuals with young onset PD, a population known to have slower disease progression and less cognitive impairment (Schrag et al., 1998).

Another potential caveat is the lack of a control group limiting the generalisation of our findings. Diagnostic accuracy can also be a problem in research with ICBs. On the one hand, patients and relatives commonly under-report ICBs, either because of lack of insight or concealment (Averbeck et al., 2014). On the other hand, using only screening tools such as the QUIP can result in a large number of false positive cases (Papay et al., 2011). The approach to diagnose ICBs used in this study, interviews at both visits aided by screening questionnaires, likely contributed to accurate detection of ICBs. Furthermore, spouses/carers were interviewed when available and all patients were seen by movement disorders specialists with research interest in ICBs.

2.5 Conclusion

In this eight-year follow up study of ICBs in PD, a lower rate of remission than previously reported and higher proportion of multiple ICBs were found. ICBs can remain troublesome for many in the long term and are associated with significant reduction in quality of life and increased prevalence of depression. Despite this, all but one patient showed some improvement after reduction of dopaminergic treatment. The most used treatment strategy was cessation of oral/transcutaneous DA, but approximately half of the patients were still using these drugs at follow up. Even when reduction or discontinuation of oral/transcutaneous DA was possible it did not guarantee long-term remission.

Chapter 3: Expanding the clinical knowledge on impulsive compulsive behaviours in Parkinson's disease

3.1 Compulsive sexual behaviour in Parkinson's disease is associated with higher doses of levodopa

3.1.1 Introduction

ICBs are a significant source of distress for patients with PD and their families. Among the different types of ICBs, CSB is particularly difficult to diagnose, considering the obvious sensitive and personal nature of sexual behaviour, and it is likely that prevalence numbers are under reported. While the prevalence of CSB in the general population is 3 to 6% (Nakum and Cavanna, 2016), previous research estimates the lifetime prevalence of this abnormal behaviour in individuals with PD between 2 and 3.9% (Weintraub et al., 2010a, Voon et al., 2006a, Weintraub et al., 2006). Similar to what has been found for other ICBs, the prevalence of CSB is higher among PD patients on DA, reaching 7.4% (Nakum and Cavanna, 2016). CSB has also been associated with male gender and earlier onset of PD (Nakum and Cavanna, 2016). Whilst the use of DA has been linked to development of CSB, and levodopa has been associated with ICBs in general (Weintraub et al., 2010a), it is still unclear whether higher doses of levodopa are a risk factor for the development of CSB in PD patients.

3.1.2 Materials and methods

Patients were identified from a database of individuals with PD and ICBs who were seen at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, and who had participated in 3 previous research projects over an eight-year period (from 2008 to 2016). Each project received approval by the local ethics committee. All the ICB cases were recruited to research studies from PD clinics at the National Hospital and selected due to the reporting of ICBS. All the 46 patients who participated in the study described in

chapter 2 (The long-term outcome of impulsive compulsive behaviours in Parkinson's disease) were included.

All cases underwent a thorough clinical investigation as well as a detailed semi-structured interview conducted by a movement disorders specialist. Hospital notes were reviewed for clinical and demographic data, with particular interest in dopaminergic treatment when ICBs were diagnosed. LEDD was calculated according to previously published guidelines (Tomlinson et al., 2010). Data was analysed using the software SPSS 22, all variables were tested for normality and statistical tests chosen accordingly.

3.1.3 Results

In total, 128 PD+ICB were identified. Seventeen cases were excluded because data on dopaminergic treatment when the ICB was most active was incomplete. The remaining 111 patients were included in the analysis. Just over 75% of the patients were males. The average age of PD onset for the entire cohort was 46.3 years, mean PD duration 11.3 years and mean age at ICBs 56.9 years. DA were used by 91% of the patients (table 8 on page 58).

Only 9 patients were not exposed to DA: 2 with isolated DDS; 1 with isolated compulsive eating; 1 with isolated pathological gambling; 1 with DDS associated with compulsive shopping and punding; 1 with DDS, CSB and punding; 1 with CSB and pathological gambling; 1 with pathological gambling and compulsive shopping; and 1 with CSB and compulsive shopping.

CSB was the most frequently identified ICB, present in 49.5% of the patients. Details on the prevalence of other types of ICBs can be seen in table 8. Multiple ICBs were present in 69 patients (62.1%).

Table 8. Clinical and demographic data	
N	111
Proportion of males	76.8%
Mean age of PD onset in years	46.3 (± 10.2; 21 – 66)
Mean PD duration at onset of ICBs in years	11.3 (± 6.8; 1 – 43)
Mean age at ICBs onset in years	56.9 (± 9.5; 33 – 75)
Patients using a dopamine agonist	91%
Total LEDD in mg	1280.8 (± 630; 120 – 3460)
Types of ICBs	
Compulsive sexual behaviour	55 (49.5%)
Punding	48 (43.2%)
Compulsive shopping	43 (38.7%)
Pathological gambling	36 (32.4%)
Dopamine dysregulation syndrome	27 (24.3%)
Compulsive eating	22 (19.8%)

Clinical and demographic data of the entire cohort. PD – Parkinson's disease; LEDD – levodopa equivalent daily dose; ICBs – impulsive compulsive behaviours. Results expressed in total values and/or proportions or mean values with standard deviation and range.

For statistical analysis, the cohort was divided into two groups based on the presence of CSB: PD+CSB (N = 55) and PD-CSB (N = 56). The proportion of male individuals was higher in the PD+CSB group and these individuals developed ICBs at a younger age (table 9 on page 60).

There were no differences between groups in the proportion of patients using levodopa, DA, MAOi, amantadine or COMT inhibitors (COMTi). Nine patients had not been exposed to DA, 3 with CSB and 6 without. The PD+CSB group was using a higher dose of dopaminergic treatment and levodopa as measured by total LEDD, levodopa daily dose, combined levodopa and COMTi LEDD, and isolated COMTi LEDD. DA LEDD and MAOi LEDD were similar between groups. Multiple ICBs were present in 48.2% of individuals without and 76.3% of individuals with CSB ($p = 0.002$) (table 9).

There was no difference in the number of patients with DDS between groups, showing that the higher dose of levodopa in the PD+CSB group was not being driven by a higher proportion of dysregulators. The prevalence of other ICBs was also similar between groups (table 9).

Table 9. Comparison of clinical and demographic characteristics

	PD+CSB	PD-CSB	p
N = 111	55	56	
Proportion of males (%)	94.5	60.7	**<0.001***
Age of PD onset (years)	44.6	48.0	0.079**
PD duration (years)	11.8	13.2	0.344**
PD duration at ICB onset (years)	10.8	11.8	0.471**
Age at ICB onset (years)	54.6	59.1	**0.020****
Multiple ICBs (%)	76.3	48.2	**0.002***
Patients using levodopa (%)	98.1	91	0.206*
Patients using DA (%)	94.5	89.2	0.48*
Patients using MAOi (%)	36.3	26.7	0.312*
Patients using amantadine (%)	49	44.6	0.705*
Patients using COMTi (%)	49	53.5	0.706*
Levodopa daily dose (mg)	994.5	704.9	**0.043****
DA LEDD (mg)	385	357.8	0.802**
MAOi LEDD (mg)	97.5 (N=20)	96.67 (N=15)	0.934**
Levodopa + MAOi LEDD (mg)	911.5 (N=20)	696.7 (N=15)	0.114***
COMTi LEDD (mg)	265.2 (N=27)	215.6 (N=30)	**0.026****
Levodopa + COMTi LEDD (mg)	1068.5 (N=27)	874.5 (N=30)	**0.039****
Total LEDD (mg)	1400.1	1163.6	**0.014****
Types of ICBs			
Punding	38.1	48.2	0.340*
Compulsive shopping	43.6	33.9	0.333*
Pathological gambling	30.9	33.9	0.840*
Dopamine dysregulation syndrome	21.8	26.7	0.659*
Compulsive eating	14.5	25	0.234*

*Comparison of clinical and demographic characteristics between groups. PD – Parkinson's disease; ICBs – impulsive compulsive behaviours; DA – dopamine agonist; MAOi – monoamine oxidase inhibitor; COMTi – COMT inhibitor; LEDD – levodopa equivalent daily dose. *Chi-square test. Results expressed in total values or proportions. **Mann-Whitney U test. Significant results in bold.*

3.1.4 Discussion

Most of the patients in this cohort comprised men, which is in keeping with previous studies (Weintraub et al., 2010a). CSB was the most frequently identified ICB in our cohort, affecting almost 50% of individuals with PD-associated ICBs. A novel finding was that PD+CSB tend to develop this abnormal behaviour at an earlier age and are more likely to develop multiple ICBs compared to PD patients with other ICBs. This finding has important clinical implications as individuals with multiple ICBs are more likely to develop depression (Wu et al., 2015) and higher levels of impulsivity have been associated with worse quality of life in PD (Leroi et al., 2012a). Furthermore, considering the high prevalence of CSB found and the possibility of under-reporting, clinicians should specifically enquire PD patients about this behaviour, particularly if other ICBs are present.

The prevalence of multiple ICBs in this cohort was nearly two thirds, higher than the 28.7% of PD+ICB found by Weintraub and colleagues (Weintraub et al., 2010a), similar to the prevalence found by Garcia-Ruiz analysing PD patients on DA (Garcia-Ruiz et al., 2014), and lower than the 80% found by Poletti and collaborators (Poletti et al., 2013). The different numbers reported might be a consequence of the different instruments used to diagnose ICBs, as it has been reported that the QUIP can be positive in up to 40% of patients without a diagnosis of ICB (Papay et al., 2011). The figures reported here seem accurate as all patients were seen in a research setting and diagnosed by a movement disorders specialist with the aid of a semi-structured interview in combination with the QUIP, after it became available. Furthermore, all patients seen in this study had significant impairment in social or occupational functioning from the abnormal behaviours.

Between group analysis showed that the two groups had similar age at PD onset and disease duration, however the proportion of male patients was significantly higher in the PD+CSB group. This is in line with the literature as other authors have also found that CSB is more likely to develop in male PD patients (Weintraub et al., 2010a, Voon et al., 2006a). The menopause is responsible for a decline in the sexual function of healthy women (Avis et al.,

2017) and could theoretically contribute to the lower prevalence of CSB in women with PD, but larger studies are needed to answer this question. Cultural bias could also make women less likely to report CSB. Younger age of PD onset is a well-known risk factor for the development of ICBs and many authors have published data on this positive association (Djamshidian et al., 2011a). However, this is the first study to report that patients with PD and CSB tend to develop this abnormal behaviour at an earlier age compared to patients with other ICBs.

Another novel finding is that PD+CSB were on higher doses of dopaminergic treatment. The majority of patients were using a dopamine agonist, in keeping with previously published data that shows that DA are the main risk factor for the development of ICBs (Weintraub et al., 2010a, Giladi et al., 2007, Voon et al., 2007). DA and MAOi dose, measured in LEDD, and the proportion of patients using DA, amantadine and MAOi did not differ. However, patients with CSB were using higher levodopa daily dose and higher COMTi doses than patients without CSB, although the proportion of patients using COMTi did not differ between groups. This suggests that higher dopaminergic stimulation, particularly higher doses of levodopa are a risk factor for the development of CSB. It is likely that higher doses of COMTi are not directly related to ICBs but, rather, are contributing to excessive dopaminergic stimulation by increasing the bioavailability of levodopa. This is corroborated by the fact that only half of the patients were using COMTi.

The association of abnormal sexual behaviour and levodopa was reported in the early days of levodopa use, years before DA started being used for PD. Barbeau and colleagues treated 80 patients with PD with an average dose of 4.8 g of levodopa per day and reported that at least 4 males developed an increase in libido (Barbeau, 1969). Corroborating this finding, levodopa has been shown to increase mounting behaviour in male rats. Dopamine's facilitatory role in the sexual behaviour of male rats, which appears to also be present in male primates, can explain these findings and the association of CSB with higher doses of levodopa (Melis and Argiolas, 1995).

Although the main risk factor for the development of impulse controls disorders in PD is the use of DA (Weintraub et al., 2010a), levodopa has been found to be an important contributor to the development of ICBs in patients already receiving treatment with DA (Hassan et al., 2011). Higher doses of levodopa are the most important risk factor for the development of DDS in PD patients (O'Sullivan et al., 2009). Punding has also been associated with higher doses of levodopa (Evans et al., 2004), although it is also significantly associated with DA use (Pettorruso et al., 2016). This is in contrast to pathological gambling, which rarely occurs on levodopa monotherapy (Djamshidian et al., 2011b). Data from animal models have shown that chronic levodopa use can result in ectopic expression of D3R that could theoretically facilitate appearance of behavioural problems through sensitization (Luquin-Piudo and Sanz, 2011). More data is needed to answer whether levodopa is the direct cause for the development of CSB or is acting through behavioural sensitization.

Interestingly, despite finding that patients with CSB were on higher doses of levodopa, the proportion of other types of ICBs was similar between groups, indicating that even though higher levodopa doses are associated with both CSB and DDS, these abnormal behaviours are not more likely to occur together. This finding also suggests that the higher doses of levodopa being used by PD+CSB were not being driven by patients with DDS. Another important clinical implication from this study is that clinicians that are confronted with patients with CSB must be aware that increasing levodopa (to compensate for reducing the DA dose) may also be associated with increased risk of CSB.

By including only patients who participated in previous research projects, it is possible that patients with ICBs that were diagnosed during a regular outpatient's appointment were not included. However, since the idea was to assess the prevalence of CSB among patients with established ICBs, it is likely that this approach minimised the possibility of including false positives.

It is possible that the association of CSB with higher doses of levodopa was found by chance, and more studies are needed to confirm this finding. In addition, this retrospective case control study does not allow causality

correlations. Nonetheless, this study highlights the potential behavioural complications of increased dopaminergic treatment.

3.1.5 Conclusion

The data from this study confirms that CSB is more frequent in males and tends to appear earlier than other ICBs. CSB may be the most frequent ICB associated with PD. Furthermore, patients with CSB are more likely to develop multiple ICBs. When compared to other types of ICBs, this behavioural addiction appears to be driven by higher doses of levodopa. Data from larger studies are needed to confirm these novel findings.

3.2 The outcome of dopamine dysregulation syndrome in Parkinson's disease: a post mortem study

3.2.1 Introduction

DDS is characterised by compulsive dopaminergic medication use markedly exceeding the amount required for adequate control of PD symptoms (O'Sullivan et al., 2009). The main risk factors for the development of DDS are male sex, younger age at PD onset and dopaminergic treatment (Djamshidian et al., 2011a, Giovannoni et al., 2000, Katzenschlager, 2011). Patients with DDS also commonly develop concomitant ICBs, depression and an altered perception of ON state (Giovannoni et al., 2000, Cilia et al., 2014). Some patients describe 'a high' from each dose of levodopa initially but go on to crave and want higher and higher doses without any liking or enjoyment from their therapy. The behavioural sequelae closely resemble those experienced by chronic cocaine and amphetamine addicts (Volkow et al., 2004).

A carefully supervised slow reduction in the daily dose of levodopa can lead to improvement or resolution in some patients. However, despite adequate treatment, a follow up study over several years has previously reported that more than a third of patients remain symptomatic (Cilia et al., 2014).

Considering that DDS is an uncommon complication of dopaminergic treatment and the relative paucity of literature on this topic, more data is needed to guide clinical care. This section describes a retrospective analysis to assess the prevalence, association with medication, clinical characteristics and outcome of DDS in a population of pathologically proven PD patients from the Queen Square Brain Bank for Neurological Disorders (QSBB), London, UK.

3.2.2 Materials and methods

A QSBB database search for consecutive donations from 2005 to 2016 with a diagnosis of PD was performed. Thirty-two cases from the cohort described in chapter 5 (Impulsive compulsive behaviours in Parkinson's disease are associated with lower alpha-synuclein load and dopamine D3 receptor levels in the nucleus accumbens) were included: 15 PD+ICB and 17 PD-ICB. All cases of PD who developed DDS according to previously published diagnostic criteria (Giovannoni et al., 2000) underwent detailed review of GP and hospital records. Sex, age at PD onset, PD duration and age at death were collated, as well as presence of dementia, depression and dyskinesias. For those with DDS, additional data was collected, particularly duration, medications associated with the development of DDS, dose of dopaminergic treatment at DDS onset and death, use of DA and the outcome of DDS.

All variables were tested for normality and statistical tests chosen accordingly. Data was analysed using SPSS 22. The QSBB has a license from the Human Tissue Authority to store brain tissue and its brain donation protocols were approved by a London Multi-Centre Research Ethics Committee. Written consent for donation was obtained from all cases.

3.2.3 Results

A total of 193 cases with a pathological diagnosis of idiopathic PD among brain donations received from 2005 to 2016 were identified (124 males and 69 females). The average age at disease onset was 60.2 years, the average age at death was 77.5 years and average disease duration 17.3 years. Dementia occurred in 46% of the patients, depression in 24.4% and levodopa-induced

dyskinesias in 42%. Seventeen patients developed DDS. Of these, 10 died of pneumonia, 2 of myocardial infarction, 2 of PD, 1 from heart failure, 1 from dissecting aortic aneurysm and 1 from malnutrition.

For statistical analysis, patients were divided into two groups based on the presence of DDS: PD+DDS (patients with PD and DDS) and PD-DDS (patients with PD without DDS). Eleven PD-DDS had ICBs other than DDS: 8 CSB, 1 compulsive shopping, 1 pathological gambling and 1 CSB and punding. PD+DDS had younger age at PD onset, higher prevalence of dyskinesias, longer disease duration, and died at an earlier age compared to PD-DDS (table 10 on page 67). The majority of patients who developed dyskinesias (78%) did so before DDS.

A few observations from patients' notes are included to illustrate the phenomenology of DDS: "daughter noticed that her mother was taking sinemet like 'smarties'"; "patient is using more levodopa than necessary but prefers to run high with some dyskinesia"; "patient is stockpiling medication, taking 2125 mg of levodopa per day but stated he was on 1350 mg"; "phoned because he had used all levodopa, confessed he was using excessive medication that was making him feel disturbed, agitated and dyskinetic"'; "when ON patient was hyperactive and slightly maniac and when OFF depressed, during admission was clearly ON but claimed to be OFF"; "patient's assessment of OFF-periods were rather inaccurate"; "grossly dyskinetic due to the fact that he takes his drugs at will, took own discharge during hospitalisation to reduce levodopa and went back to previous doses".

All patients with DDS received neurological and psychiatric care and 8 of them were seen at the National Hospital for Neurology and Neurosurgery, Queen Square. The average duration of DDS was 53.5 months. One patient in the PD+DDS group had undergone implantation of embryonic mesencephalic tissue 3 years before developing DDS.

Table 10. Comparison between groups

	PD+DDS (N = 17)	PD-DDS (N = 176)	P
Males (%)	14 (82.3%)	110 (62.5%)	0.119*
Age at PD onset (years)	50.8 (± 9)	61.2 (± 10.7)	**<0.001****
Disease duration (years)	22.5 (± 5.7)	16.7 (± 8)	**0.003*****
Age at death (years)	73.4 (± 8)	77.9 (± 7.6)	**0.020*****
Dementia (%)	7 (41.1%)	82 (46.5%)	0.669*
Depression (%)	7 (41.1%)	40 (22.7%)	0.134*
Dyskinesias (%)	14 (82.3%)	67 (38%)	**0.001***

*Comparison between PD patients with (PD+DDS) and without DDS (PD-DDS). PD – Parkinson's disease; DDS – dopamine dysregulation syndrome. Results expressed in mean values and standard deviation or total values and proportions. Significant results in bold. *Chi-square test; **unpaired t-test; ***Mann-Whitney U test.*

Five of the patients with DDS had concomitant ICBs (4 CSB and 1 pathological gambling). All PD+DDS were using levodopa at onset, albeit only 3 (17.6%) as monotherapy. Details of other anti-parkinsonian medications are shown in table 11 on page 69. The amount of dopamine replacement therapy in LEDD was calculated as previously described (Tomlinson et al., 2010). Although patients were using less medication at the time of death in comparison to peak usage, this did not reach statistical significance ($p = 0.356$; Wilcoxon matched pairs).

Nine out of seventeen patients (52.9%) improved completely, 7 (41.1%) partially and in 1 patient (5.8%) DDS remained unchanged until death. All patients had alteration of their dopaminergic medication as a therapeutic measure. Levodopa dose was reduced in 10 cases; cessation of DA was done in 4 cases and reduction of DA dose in 3.

Further statistical tests comparing patients who achieved remission with patients who remained symptomatic until death demonstrated a trend for higher levodopa lifetime cumulative dose (calculated as described elsewhere (Parkkinen et al., 2011)) in the latter group but this failed to reach statistical significance. LEDD at DDS onset and at death, as well as duration of DA treatment, did not differ between groups. However, patients who failed to achieve remission were exposed to higher DA doses (table 11).

Table 11. Characteristics of the patients who developed DDS			
	PD+DDS (N = 17)		
Average duration of DDS (months)	53.5 (± 65.6)		
Medications at DDS onset			
Levodopa	17 (100%)		
Oral/transdermal DA	10 (58.8%)		
Selegiline	5 (29.4%)		
Amantadine	3 (17.6%)		
Apomorphine infusion	2 (11.7%)		
LEDD at DDS onset	1411 (± 579)		
LEDD at death	1196 (± 636)		
Outcome	**Remission (N = 9)**	**Partial improvement /unchanged (N = 8)**	**p value**
Levodopa lifetime cumulative dose	3643 kg (± 3517)	5837 kg (± 3468)	0.083*
LEDD at DDS onset	1468 (± 595)	1346 (± 595)	0.680*
LEDD at death	1225 (± 797)	1164 (± 444)	0.564*
DA peak LEDD	229.4 (± 94) N = 7	429.1 (± 224.7) N = 7	**0.035***
DA duration in months	86 (± 26.2) N = 7	83.7 (± 55.5) N = 7	0.620*

*Characteristics of the patients who developed DDS and comparison according to remission status. DDS – dopamine dysregulation syndrome; DA – dopamine agonist; LEDD – levodopa equivalent daily dose. Results expressed in mean values and standard deviation or total values and proportions. Significant results in bold. *Mann-Whitney U test.*

3.2.4 Discussion

This is the longest follow up study of DDS in pathologically proven PD patients who received specialist care during life. The overall prevalence of DDS was 8.8%, which is higher than previously reported (Katzenschlager, 2011, Giovannoni et al., 2000). No particular effort was made at the QSBB to seek donation from patients known to have DDS in life. The longer length of follow up in this group of patients raises the possibility that the lifetime prevalence of DDS may be higher than has hitherto been recognised. An alternative explanation is that patients with DDS were more likely to donate their brains because of increased impulsivity levels (Averbeck et al., 2014).

Patients with DDS had earlier disease onset (Warren et al., 2017) and longer disease duration. This likely reflects the predominance of younger patients, who tend to experience slower progression of PD (van Rooden et al., 2010). However, DDS patients died at a younger age than patients without DDS, probably reflecting the earlier age of onset. Pneumonia was the main cause of death among PD+DDS and there were no suicides (Pennington et al., 2010).

A total of 41% of patients developed dementia after DDS, in line with a recent study (Williams-Gray et al., 2013) and confirming previous findings that patients with DDS are not more likely to develop dementia (Cilia et al., 2014). Depression was present in approximately 24%, also consistent with the literature (Reijnders et al., 2008). The retrospective data collection, the small sample size and the fact that most patients were not formally assessed for depression might have contributed to a lower prevalence of depression than expected from clinical observation.

As expected, dyskinesias were more prevalent in PD+DDS in part reflecting the higher levodopa dosage. A recently published study found that patients with PD and dyskinesias have a higher prevalence of ICBs than a general PD population, raising the possibility of dopaminergic sensitisation as a shared mechanism between both phenomena (Biundo et al., 2017, Voon et al., 2009). The fact that dyskinesias tended to predate DDS suggests that PD patients at risk who develop dyskinesias should be carefully screened for DDS. Only about

a third of the patients with DDS had other ICBs, which is lower than in a recent systematic review (Warren et al., 2017).

At the time of DDS diagnosis all patients were using levodopa, but only 3 as monotherapy. Levodopa is believed to be the main risk factor for the development of DDS (O'Sullivan et al., 2009). DA were used as an add on therapy by more than 50% of the patients with DDS, in line with a recent review (Warren et al., 2017). Apomorphine infusion was used by 2 patients at DDS onset. Apomorphine is a dopamine agonist with a different pharmacological profile than other DA, as it stimulates mainly D1R and D2R (Fahn et al., 2011b), akin to levodopa. Studies of PD patients on apomorphine infusion suggest a lower prevalence of ICBs compared to oral DA (Magennis, 2012, Martinez-Martin et al., 2014, Todorova et al., 2015) but it is still unclear whether apomorphine use is associated with increased risk of DDS. Continuous delivery of dopaminergic drugs may have less reinforcing properties resulting in a lower risk for triggering DDS (Katzenschlager, 2011). In this study, 3 patients used infusion therapies, 2 apomorphine infusion and 1 duodopa, and in all DDS resolved.

Although nearly all the patients showed some improvement after phased reduction in dopaminergic treatment, nearly half of them remained symptomatic until death. This is a similar remission rate to a systematic review on DDS (Warren et al., 2017) and higher than a long term retrospective study (Cilia et al., 2014). Interestingly, patients who remained symptomatic were exposed to higher maximum doses of DA. It is possible that excessive stimulation of D3R might act to sensitise the ventral striatum to the reinforcing properties of levodopa. It is important to note that peak DA dose was calculated based on doctor's notes, and there is a possibility that doses were understated. Nonetheless, the association of peak DA dose with persistent DDS has not been reported previously and further studies are needed to confirm this finding.

The main disadvantage of this study is that, as with many brain bank studies, the clinical information was analysed retrospectively, making quality of data heavily dependent on the details provided in the hospital records. However, all

patients were seen by consultant neurologists regularly and the clinical detail provided in the notes was substantial.

3.2.5 Conclusion

The prevalence of DDS in a brain bank study of Parkinson's disease raises the possibility that one in eleven patients may develop DDS. Treatment success depends critically on the ability to achieve concordance in dopaminergic drug dose reduction.

3.3 Cognitive and neuropsychiatric profile of punding in Parkinson's disease

3.3.1 Introduction

Punding is a stereotyped non-goal orientated behaviour, characterized by repetitive manipulations of technical equipment, the continual handling, examining, and sorting of common objects, grooming, hoarding, pointless driving or aimless walkabouts (Evans et al., 2004). Initially described among amphetamine and cocaine users, punding was first reported in a levodopa treated patient with PD by Friedman in 1994 (Friedman, 1994). The prevalence of punding in PD varies between 1.4% (Miyasaki et al., 2007) up to 14% of patients (Evans et al., 2004).

There is an idiosyncratic quality to punding, with previous occupations and pre-morbid hobbies influencing the type of abnormal behaviour (Evans et al., 2004). Patients with punding have more psychiatric symptoms, greater impulsivity and are more likely to have other ICBs (Pettorruso et al., 2016). Punding has also been linked with DDS (Evans et al., 2004) and levodopa peak dose dyskinesias (Silveira-Moriyama et al., 2006).

Little is known about the neuropsychiatric profile of patients with punding. In this study, clinical and neuropsychiatric features of PD patients with punding/hobbyism were compared to PD-ICB.

3.3.2 Materials and methods

A total of 47 PD patients diagnosed with punding and/or hobbyism and 25 PD patients without punding or other ICBs were recruited from a movement disorders outpatient clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. Eighteen patients with punding described in chapter 2 (The long-term outcome of impulsive compulsive behaviours in Parkinson's disease) were included in this study, as well as 9 PD+ICB and 15 PD-ICB from chapter 4 (Impaired saccadic suppression in patients with Parkinson's disease and impulsive compulsive behaviours).

A diagnosis of punding/hobbyism was made based on the QUIP-RS using previously published cut-off scores (Weintraub et al., 2012) and confirmed with a structured interview. PD-ICB also completed the QUIP-RS and structured interview to confirm the absence of punding or other ICBs. Participants self-completed the following questionnaires: the HADS, the SF36, the Barratt Impulsiveness Scale (BIS11), the REM Sleep Behaviour Disorder Screening Questionnaire (RBDq) and the Apathy Scale (AS). The UPDRS parts I and III, AIMS, FAB, MoCA, and the Stroop test (EncephalApp Stroop Test (Bajaj et al., 2013)) were completed with the investigating physician.

The study received approval by the local ethics committee. All variables were tested for normality. Parametric data was analysed using independent samples t-test and non-parametric data Mann-Whitney U test. Proportions were compared with the Pearson chi-square test, except if the minimum expected cell count was less than five, when the Fisher's exact test was used. A p value of less than 0.05 was considered significant. Data was analysed using SPSS 22.

3.3.3 Results

Forty-seven patients with PD and punding (PD+pu) as the dominant behavioural phenotype were included in the study and compared to 25 PD-ICB. There were no differences in age, duration of illness or medication use, including amantadine and MAOi (Table 12 on page 75), as well as current total dose of levodopa or of DA. As punding has been shown to be related to high

DA doses, the current DA dose was compared to the peak DA dose and found to be 62% lower among patients with punding (Wilcoxon matched pairs; p = 0.016). In comparison, there had been a smaller non-significant reduction in DA dose in the PD-ICB group (Wilcoxon matched pairs; p = 0.176).

Among the 47 patients with punding and hobbyism, 25 had comorbid ICBs: DDS was present in 4 individuals; CSB in 16; pathological gambling in 6; compulsive shopping in 8; and compulsive eating in 13. A comparison between patients with isolated punding and punding associated with co-morbid ICBs showed no significant differences, except for HADS and UPDRS part I scores, which were significantly higher in patients with punding and other ICBs compared to isolated punding.

Table 12 shows the neuropsychiatric and cognitive characteristics of the two groups. Compared to PD-ICB, PD+Pu reported significantly higher scores on the HADS anxiety subscale. Motor fluctuations, defined as wearing-off of levodopa, absence of ON, ON-OFF phenomenon and unpredictable OFF periods, were more frequent in patients with punding. There was a trend for higher prevalence of levodopa-induced dyskinesias and RBD in the PD+pu group. None of the SF36 subscales differed between groups.

The UPDRS part I scores were significantly higher in PD patients with punding, but the UPDRS part III scores did not differ. The difference seen for UPDRS part I remained significant after correcting for the dopamine dysregulation syndrome score (unpaired samples t-test; p = 0.034) and the anxiety score (unpaired samples t-test; p = 0.015). PD+pu also showed significantly higher impulsivity levels in the BIS11 questionnaire and lower (worse) FAB scores. Patients with punding had slower reaction times on the Stroop test but made a similar number of errors compared to the control group. The MoCA scores did not differ between groups. See table 12.

Table 12. Comparison of demographic and clinical characteristics

	PD+pu (N = 47)	PD-ICB (N = 25)	p value
Male sex	38 (80.8%)	18 (72%)	0.390*
Age	57.5 (± 14)	59.8 (± 9)	0.640†
Age at PD onset (years)	44.7 (± 10.5)	47.56 (± 7.9)	0.238¥
Disease duration (years)	14.5 (± 8.5)	12.4 (± 6.7)	0.352†
Depression	22 (46.8%)	11 (44%)	0.820*
Dyskinesias	37 (78.7%)	15 (60%)	0.063*
Deep brain stimulation	5 (10.6%)	4 (16%)	0.513*
DA use	22 (46.8%)	13 (52%)	0.675*
MAOi use	9 (19.1%)	3 (12%)	0.532**
Motor fluctuations	43 (91.4%)	18 (72%)	**0.041****
LEDD[9]	1090.8 (± 426)	893.8 (± 526)	0.090¥
DA dose in LEDD	197 (± 148) N=22	257 (±127) N=13	0.132†
HADS total	17 (± 6)	13.1 (± 6)	**0.016¥**
HADS anxiety	9.3 (±3)	6.8 (± 4)	**0.014¥**
HADS depression	7.6 (± 3)	6.6 (± 3)	0.270¥
UPDRS part I	19.2 (± 8) N=44	13.2 (± 5) N=18	**0.010¥**
UPDRS part III	29 (± 11)	24.4 (± 14)	0.138¥
BIS11	67.8 (± 7) N=42	64.1 (± 6) N= 22	**0.049¥**
AIMS	7.3 (± 6)	4.8 (± 6)	0.070†
FAB	15.6 (± 2)	16.6 (± 2)	**0.017**†
MoCA	25.7 (± 5)	27.1 (± 2)	0.324†
RBD	78% N=41	50% N=20	0.064*
Apathy Scale	14.5 (± 6) N=40	13 (± 5) N=18	0.320†
Stroop reaction time (s)	19.1 (± 5.2) N=21	16.34 (± 2.3) N=12	**0.040¥**
Stroop errors	1.4 (± 2.2)	0.42 (± 0.5)	0.321†

*Comparison between groups. PD – Parkinson's disease; PD+pu – patients with PD and punding; PD-ICB – PD patients without ICBs; DA – dopamine agonist; MAOi – monoamine oxidase inhibitors; LEDD – levodopa equivalent daily dose; HADS – Hospital Anxiety and Depression Scale; UPDRS – Unified Parkinson's Disease Rating Scale; BIS11 – Barratt Impulsiveness Scale; AIMS - Abnormal Involuntary Movement Scale; FAB - Frontal Assessment Battery; MoCA - Montreal Cognitive Assessment; RBD – Rem Sleep Behaviour Disorder; Results expressed in mean values and standard deviation or total values with proportions. Significant results in bold. *Chi-square test; **Fisher's exact test; ¥ unpaired t-test; †Mann-Whitney U test.*

3.3.4 Discussion

Our findings support previous data showing that PD+pu have higher impulsivity (Pettorruso et al., 2016, Evans et al., 2004). Furthermore, punding was associated with increased anxiety and NMS, frontal lobe abnormalities on neuropsychological testing and higher prevalence of PD motor fluctuations.

Punding is more common in males who develop PD at an earlier age (Spencer et al., 2011), compatible with our findings. There were no differences in quality of life between groups, contradicting previous data (Lawrence et al., 2007). Considering that the SF36 is a self-assessment questionnaire it is possible that patients with punding failed to report difficulties due to lack of insight. Another possible explanation is that the SF36 is less sensitive to changes in PD patients as it has been designed as a general quality of life questionnaire.

PD+pu had higher levels of anxiety, which is in line with a previous study in PD+ICB (Leroi et al., 2011) but in disagreement with another study (Pettorruso et al., 2016). Although punding is not driven by anxiety per se, anxiety can develop when patients are forced to stop their behaviour against their will (Fasano and Petrovic, 2010).This may explain the higher anxiety scores at assessment. The depression scores did not differ between groups, in keeping with previous reports (Fasano and Petrovic, 2010).

The Stroop task revealed that patients with punding had longer reaction times before making a decision in line with a previous study (Yoo et al., 2015). However, error rates did not differ between the two groups, compatible with previously published data assessing PD+ICB (Djamshidian et al., 2011c). The longer reaction time may reflect delayed decision making and frontal lobe dysfunction. Interestingly, prefrontal cortical thinning on neuroimaging has been described in PD+pu (Yoo et al., 2015, Markovic et al., 2017).

Supporting the evidence for frontal lobe dysfunction, patients with punding scored lower than controls on the FAB. Contradictory data from PD+ICB have been published (Averbeck et al., 2014) but no previous studies have specifically assessed frontal function in PD+pu. It has been postulated that the abnormal

expression of stereotypic behaviours is associated with frontal lobe dysfunction (Fasano and Petrovic, 2010), which could explain the lower FAB scores. Furthermore, punding also occurs among individuals addicted to cocaine and methamphetamine (Rusyniak, 2011), conditions that have been associated with frontal dysfunction (Koob and Volkow, 2010).

Higher doses of dopaminergic therapy have been consistently associated with punding (Evans et al., 2004, Spencer et al., 2011) but data on the use of DA is less clear with different groups publishing contradictory findings (Pettorruso et al., 2016, Silveira-Moriyama et al., 2006). PD+pu were not using higher doses of DA, suggesting that D3R stimulation associated with the use of DA is not the main mechanism underlying punding. Previous data shows that punding is more commonly seen in patients using drugs that stimulates dopamine D1 and D2 receptors (Fasano and Petrovic, 2010) such as levodopa. However, patients with punding had been submitted to a significant reduction in DA dose as shown by a post hoc analysis and it is possible that an assessment conducted in an earlier time point could have revealed significant differences in total dose of dopaminergic therapy and higher DA dose in the punding group.

Complex interactions between pharmacological and non-pharmacological factors (such as personal habits, personality and PD degeneration) are likely contributing to the development of punding (Fasano and Petrovic, 2010). The idiosyncratic nature of this behavioural condition and its association with compulsive symptoms (Evans et al., 2004) are arguments in favour of this idea.

Our sample size is relatively small. This is because stringent criteria were used and only PD patients who had either no evidence of punding or any other ICBs or had punding or hobbyism as the dominant phenotype were included. Nonetheless, this is one of the largest studies looking into cognitive and neuropsychiatric features of punding in PD.

3.3.5 Conclusion

Higher self-rated impulsivity associated with clinician-assessed impaired frontal function in patients with punding was reported. Peak DA doses were significantly higher than current DA dose in the PD+pu group due to physician driven dose reduction in order to manage drug induced complications. Higher dopaminergic stimulation in individuals with reduced inhibitory control could be the mechanism behind punding behaviour.

3.4 Retrospective study of impulsive compulsive behaviours in Parkinson's disease patients treated with apomorphine infusion

3.4.1 Introduction

ICBs can have devastating consequences on the lives of patients with PD and their families. The greatest risk factor for triggering these addictive behaviours is DA therapy (Weintraub et al., 2010a, Voon et al., 2007). Immediate release orally active agonists appear to carry increased risk for ICBs when compared to transdermal or prolonged release oral agonists (Garcia-Ruiz et al., 2014, Rizos et al., 2016).

The association of ICBs with oral dopamine D2/D3 agonists is well documented but the potential of apomorphine to induce them is unclear, with conflicting results reported. One study showed that in five out of seven patients, pre-existing ICBs improved after apomorphine pump therapy (5 partially and 2 completely). However, there was onset of *de novo* ICBs in six other cases (CSB, compulsive eating, compulsive shopping and internet use) using apomorphine pump therapy. Only two patients with new onset ICBs were using a DA, in both cases rotigotine (Todorova, 2013). Other studies, of 15 and 30 individuals respectively, reported no ICBs or improvement of ICBs after treatment with apomorphine (Todorova et al., 2013, Magennis, 2012). In the present study, a detailed review of clinical notes was performed to assess whether apomorphine can trigger or improve ICBs in PD.

3.4.2 Materials and methods

A retrospective audit of PD patients treated with apomorphine pumps at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, was conducted. Only patients who were registered using the apomorphine pump in the years of 2013 and 2014 were included to ensure complete data acquisition and importantly covering a period when all patients would have been questioned carefully about ICBs. Two patients described in chapter 2 (The long-term outcome of impulsive compulsive behaviours in Parkinson's disease) were included.

All files were reviewed and screened for ICBs and other neuropsychiatric disorders, including depression, anxiety, psychosis and cognitive impairment. Clinical indications for apomorphine, the daily dosage, side effects, pre-existing ICBs and therapies were noted as well as the therapeutic outcome. Data was analysed using SPSS 22.

3.4.3 Results

A total of 28 patients (18 males) were included in this study. Demographic characteristics are summarised in table 13 on page 80. All patients started apomorphine because of refractory motor fluctuations with significant off periods for at least 2 hours per day. Five patients (17.9%) discontinued the pump for the following reasons: technical problems with the pump (3 patients); hypersomnolence (1 patient); and deteriorating cognition (1 patient). The data of the 5 patients who discontinued apomorphine was included in the analysis.

Table 13. Demographic characteristics and side effects from apomorphine

	N	Range or %	SD
Number of patients	28		
Male/Female	18/10		
Mean age at PD onset (years)	51	35 - 76	± 8.8
Mean disease duration (years)	18.6	8 - 35	± 6.2
Mean disease duration when starting apomorphine (years)	15.2	6 - 28	± 5.4
Mean duration of apomorphine treatment (months)	43.3	2 - 120	± 34.6
Mean hours per day on apomorphine	13.9	12 - 24	± 3
Mean maximum apomorphine dosage (mg)	56.3	24 - 96	± 23.4
Patients who stopped apomorphine (n)	5	(17.9%)	
Patient experiencing side effects	25	(89.3%)	
Skin nodules	13	(46.4%)	
Hypersomnolence	10	(35.7%)	
Cognitive impairment	8	(28.5%)	
Visual Hallucinations	6	(21.4%)	
Dizziness	5	(17.8%)	
Postural hypotension	5	(17.8%)	
Bruising injection site	4	(14.3%)	
Nausea	2	(7.1%)	
Excessive sweating	2	(7.1%)	
Dry mouth	1	(3.6%)	
Itching injection site	1	(3.6%)	

Demographic data and side effects from apomorphine infusion. PD – Parkinson's disease; N – total number; SD – standard deviation.

Patients were divided into two groups based on the presence or absence of ICBs prior to the start of apomorphine and were followed up for a mean period of 43 months. ICBs were diagnosed by a movement disorder specialist. Follow-up visits were conducted in the same clinical setting. Twelve patients had experienced ICBs prior to apomorphine use, with more men affected than women. Eight patients had more than one ICB. Furthermore, PD+ICB had a younger onset of PD compared to PD-ICB. Both groups had similar disease duration and duration of apomorphine treatment. There was no significant difference in apomorphine dosage between the two groups, as well as occurrence of side effects. Four PD-ICB patients and one PD+ICB patient stopped apomorphine prematurely ($p = 0.25$) (Table 14 on page 82).

In total, 19 out of the 28 patients (67.8%) were treated with a DA prior to apomorphine. Five PD-ICB patients were still using a DA after initiation of apomorphine pump treatment. Six out of 12 PD+ICB patients experienced complete resolution of their ICBs and/or addictive behaviours after reduction (N = 2) or withdrawal (N = 4) of the DA (see Figure 5 on page 83), meaning that 2 PD+ICB were still using a DA after apomorphine was introduced, albeit in a smaller dose. There was no recurrence of ICBs in this group of individuals. The remaining six patients had active ICBs at the time apomorphine was started. After initiation of apomorphine pump treatment, one patient with CSB improved completely, three patients showed complete resolution of DDS and partial improvement of impulsivity (one with DDS and CSB, one with pathological gambling, and one with DDS, CSB and pathological gambling) and two patients experienced no change in their symptoms (one with hoarding behaviour and one with DDS, CSB and punding). Details on the ICBs are described in table 15 on page 84 and figure 5. One patient who had no previous history of ICBs and no previous exposure to a DA developed new onset compulsive eating approximately 15 months after starting treatment with apomorphine pump.

Table 14. Comparison between PD patients with and without ICBs

	PD+ICB (N = 12)	PD-ICB (N = 16)	p value
Male/female	11/1	7/9	**0.009***
Mean age at PD onset (years)	46.5 (± 8.1)	54.3 (± 8)	**0.018****
Mean disease duration (years)	19 (±7.8)	18.3 (± 5)	0.75**
Mean disease duration when starting apomorphine (years)	16.1 (± 6.8)	14.5 (± 4.1)	0.43**
Mean duration of apomorphine treatment (months)	39.4 (± 32.5)	46.2 (±36.9)	0.61**
Mean maximum apomorphine dosage (mg)	57.4 (± 19.9)	55.5 (± 26.4)	0.84**
Patients experiencing side effects (N)	10 (83.3%)	15 (93.7%)	0.37*
Patients who stopped apomorphine (N)	1 (8.3%)	4 (22.2%)	0.25*

*Comparison between groups. PD – Parkinson's disease; PD+ICB – PD patients with ICBs; PD-ICB – PD patients without ICBs. Results expressed in total number and proportion or mean values and standard deviation. Significant results in bold. * Chi-square test; ** t-test for independent samples.*

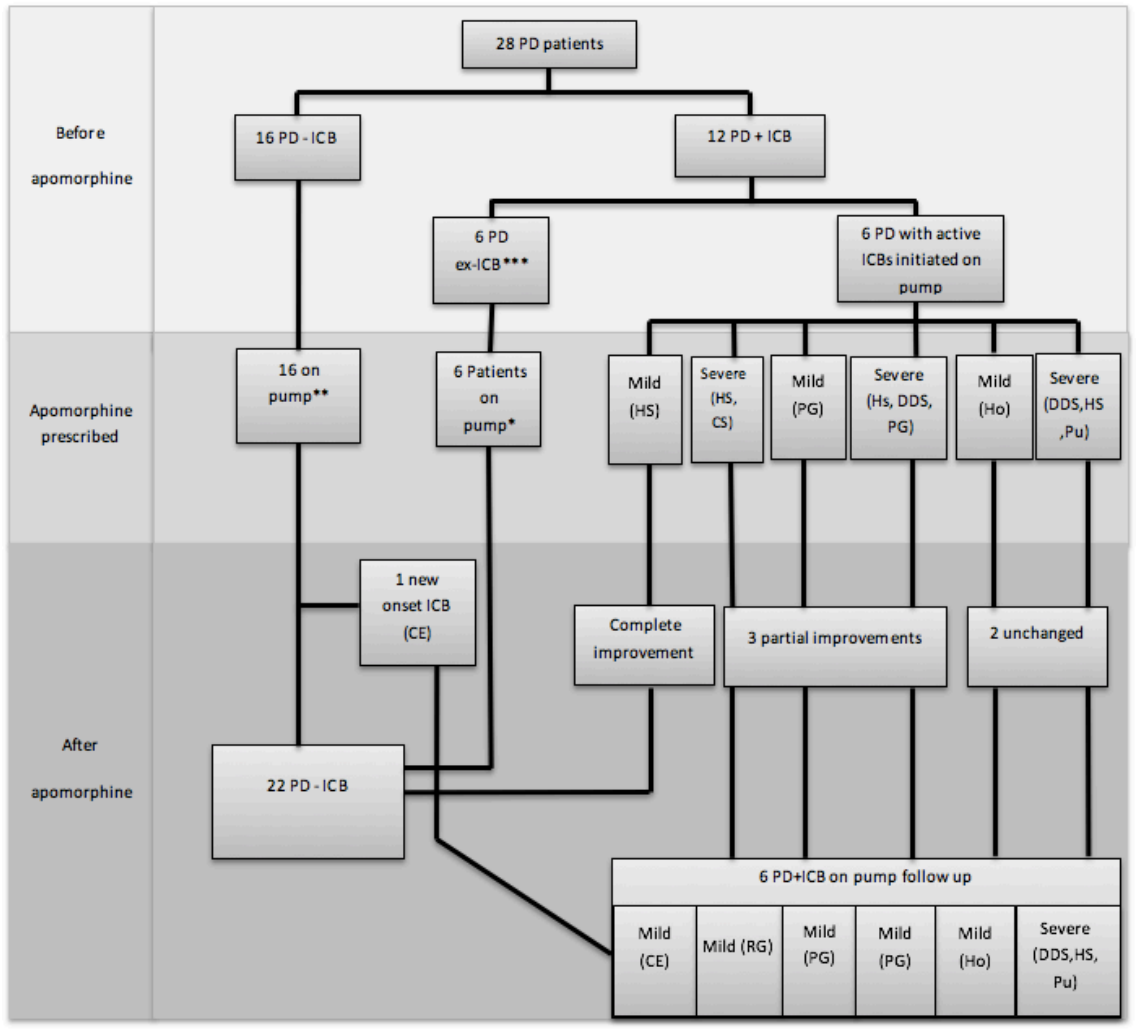


Figure 5. Outcome of patients with ICBs.

*Twelve individuals had developed ICBs (PD+ICB). Six patients improved prior to apomorphine and six remained with active ICBs. After apomorphine 3 patients had partial improvement (1 with CSB, DDS and compulsive shopping, 1 with pathological gambling and 1 DDS, CSB and pathological gambling), 1 patient with CSB improved completely, 2 patients remained unchanged (1 with hoarding and 1 with DDS, CSB and punding) and 1 patient developed de novo compulsive eating. PD-ICB – PD patients without ICBs; PD+ICB – PD patients with ICBs; CS – compulsive shopping; HS – hypersexuality; DDS – dopamine dysregulation syndrome; PG – pathological gambling; Ho – hoarding behaviour; Pu – punding; CE – compulsive eating; RG – reckless generosity. * 1 patient was also using the pen formulation. ** 2 patients were also using pen formulation. ***ICBs resolved after reduction or withdrawal of dopamine agonists.*

Table 15. Impulsive compulsive behaviours outcomes

Case	ICBs prior to apomorphine	ICBs after apomorphine	LEDD
2	DDS and CSB	ICBs resolved and did not occur.	1220
3	CSB and CS	ICBs resolved and did not occur.	1750
4	CSB, CS and punding	ICBs resolved and did not occur.	1310
5*	CSB, DDS and CS	Improved partially.	1738.5
10*	CSB	Improved completely.	1020
11*	PG	Improved partially.	1330
18	CSB and PG	ICBs resolved and did not occur.	1787.5
20*	Hoarding	ICB unchanged.	1550
24	**None**	**Compulsive eating.**	**1500**
27	CSB, CS and punding	ICBs resolved and did not occur.	1738.5
31*	DDS, CSB and PG	Improved partially. PG persisted.	1587
35*	DDS, CSB and punding	ICBs unchanged.	1510
41	CSB and PG	ICBs resolved and did not occur.	860

ICBs outcome displayed by individual cases. In bold the only case who developed de novo ICB after apomorphine infusion. ICBs – impulsive compulsive behaviours; DDS – dopamine dysregulation syndrome; CSB – compulsive sexual behaviour; CS – compulsive shopping; PG – pathological gambling; LEDD – levodopa equivalent daily dosage.

LEDD was calculated as previously described (Tomlinson et al., 2010). Considering all participants (N = 28), total LEDD was lower before apomorphine (before 1241.53; after 1414.71) (p = 0.062; Wilcoxon matched pairs test). Oral/transdermal DA LEDD for the total cohort was also calculated, which was significantly lower after apomorphine (159.2; 45.14; p = 0.01). A similar analysis in the group of patients with ICBs before apomorphine was conducted (N = 12). Although there was no difference in total LEDD before (1407.19; ±473.17) and after (1450.12; ±304.90) apomorphine treatment (p = 0.75), there was a statistically significant difference in DA LEDD before (188.98; ±170.19) and after (10.83; ±25.39) apomorphine (Wilcoxon matched pairs test; p = 0.008).

The majority of the patients (85%) had levodopa induced dyskinesias. A total of 25 patients (89.3%), experienced side effects from apomorphine, with 16 of them (57.14%) experiencing 2 or more side effects. The most common side effects were skin nodules, which occurred in 46.4% of the patients, and hypersomnolence in 35.7% (Table 13).

3.4.4 Discussion

This study suggests that apomorphine pump therapy has a lower risk of generating ICBs than oral DA treatment. All 12 patients who had ICBs prior to apomorphine had been treated with an oral DA and six of them showed complete remission of their abnormal behaviour after reducing or stopping the agonist. None of these patients experienced recurrence of ICBs after the introduction of apomorphine infusion.

Six patients still had ongoing ICBs despite reduction of DA at the time of starting the apomorphine pump. In one of these, damaging impulsivity disappeared, three more had considerable improvement so that it no longer represented a problem for the patient and to the family, and two did not experience any change in severity of their ICBs. None of these patients was still using a DA after apomorphine was started. Oral DA may induce long-term pharmacodynamic changes (van Eimeren et al., 2010), which may explain persistence of some of the pathological behaviours seen after discontinuation of treatment.

It seems probable that the reduction in DA dose was primarily responsible for the improvement seen. The fact that ICBs did not recur after apomorphine treatment initiation suggests that this drug has a lower tendency to trigger behavioural addictions in PD as previous studies have shown that attempts to reinstate oral DA, even at lower dosage, commonly lead to a recurrence of ICBs (Rabinak and Nirenberg, 2010). There are a number of potential reasons for this. There is evidence from imaging studies that large and rapid increases in extracellular dopamine may be the encoding mechanism through which dopamine attributes salience to an event in normal conditions. Dopaminergic drugs with fast brain uptake and clearance closely mimic this natural process and tend to be more implicated in the experience of “high” and drug-induced reinforcement (Volkow et al., 2004). A continuous steady state delivery of apomorphine to the dopamine receptor would have the opposite effect and may explain its low proclivity to induce addictive behaviours. Corroborating this, a recent study has shown that continuous jejunal infusion of levodopa improved DDS and other ICBs (Catalan et al., 2013). Further evidence to support this idea comes from a three-year observational study showing that infusion therapies, apomorphine and intrajejunal levodopa, carry a reduced risk for the development of ICBs in individuals with PD (Todorova et al., 2015).

Differences in affinity to dopamine receptors may also contribute to the occurrence of ICBs. Apomorphine has a receptor profile similar to dopamine with higher affinity for D1R and D2R (Fahn et al., 2011a) in contrast to other DA which have a more marked affinity for D3R. It has been suggested that this D3R selectivity may be linked to the occurrence of ICBs (Seeman, 2015, Samuel et al., 2015).

Apomorphine has also been claimed to possess sedative and anti-psychotic effects and its molecular structure includes a piperidine moiety similar to that of the major tranquiliser thioridazine (Chase and Tamminga, 1980). Historically, repeated hourly injections of apomorphine for 5 days have been used as a treatment for alcohol and other forms of substance dependence (Dent, 1952, Scheel-Kruger et al., 1977, Beil and Trojan, 1977). Neuropsychiatric symptoms have been reported to improve in some PD patients after the introduction of apomorphine pump therapy (Ellis et al., 1997), although it is unclear whether

this improvement can be a consequence of the aforementioned neuroleptic effect.

It has been suggested that ICBs and punding may be the ventral striatal equivalent to levodopa-induced dyskinesias and that both phenomena are due to dopaminergic sensitisation (Voon et al., 2009). Rodriguez-Oroz and collaborators identified a pattern of oscillatory activity in the STN in both conditions albeit in a different topography (Rodriguez-Oroz et al., 2011). The similarity between levodopa-induced dyskinesias and ICBs, coupled with the evidence that apomorphine infusion has been shown to be effective in reducing PD dyskinesias (Katzenschlager et al., 2005) may explain why none of our patients with pre-existent ICBs relapsed.

In the present study, the mean apomorphine pump dosage was 56.3 mg per day, which is lower than the 69.8 mg reported by Tyne and collaborators and the 98 mg per day reported in an earlier era from our own centre by Manson et al (Tyne et al., 2004, Manson et al., 2002). Apomorphine infusion was delivered for an average period of 13.94 hours, which is similar to the data from Tyne and collaborators, but significantly less than the 16.5 hours found by Manson et al (Tyne et al., 2004, Manson et al., 2002). It is possible that higher doses and longer duration of apomorphine may be an independent risk factor for ICBs (Antonini, 2007), therefore the lower doses used in this cohort might be another factor contributing to reduced occurrence of ICBs.

Although apomorphine appears to be safer than other DA, previous studies have shown that de novo cases of ICBs can occasionally occur in patients using apomorphine pump therapy (Martinez-Martin et al., 2014, Samuel et al., 2015, Garcia Ruiz et al., 2008). One of the patients in this cohort who had no previous history of addictive behaviours developed compulsive eating 15 months after treatment with apomorphine pump. This behaviour was mild and did not lead to a premature cessation of therapy.

The limitations of this study are that it is descriptive and retrospective and has been carried out on a relatively small number of patients, the variable follow-up period after initiation of apomorphine treatment and the relative high rate of

discontinuation of the pump. In addition, it is believed that DDS and other types of ICBs may have different pathophysiological origins. Moreover, grouping these behavioural abnormalities together limits the generalisability of these results to a wider PD population.

Considering that PD+ICB have lower insight and therefore a tendency to under-report their symptoms (Averbeck et al., 2014), it is possible that ICBs, despite being present in 46% of the cases, were still under-reported. So far, only retrospective and open-label studies have addressed the issue of apomorphine and ICBs (Samuel et al., 2015, Garcia Ruiz et al., 2008, Magennis, 2012, Todorova, 2013, Todorova et al., 2013) and the data linking DA is largely based on descriptive and epidemiological grounds.

3.4.5 Conclusion

Based on the full case notes from these patients and the research interest in dopamine dysregulation going back to 2000, apomorphine pump seems to have lower tendency to worsen or trigger ICBs. Continuous infusion of apomorphine, therefore, appears to be a valid treatment option for patients with ICBs and DDS when other treatment options have failed. Further prospective studies are needed to provide a definitive answer to this question.

Chapter 4: Impaired saccadic suppression in patients with Parkinson's disease and impulsive compulsive behaviours

4.1 Introduction

Eye movement abnormalities have been described in many neurodegenerative conditions including PD. Previous studies have included diverse methods of assessment, from physical examination by a neurologist to more sophisticated approaches, such as dedicated eye tracking devices. The known motor abnormalities characteristic of PD are reflected in saccadic movements in the form of hypometric saccades and longer fixation periods. Whilst these abnormalities have been reported in several studies, little is known about the oculomotor function of individuals with PD+ICB.

Increased reaction time (latency) and reduced gain (hypometria) of eye movements occur commonly in PD (Munoz and Everling, 2004, Matsumoto et al., 2011). Increased anti-saccadic direction errors have also been reported, even among drug-naïve patients (Antoniades et al., 2015). Although most studies have shown that voluntary (memory guided) saccades tend to be more impaired than automatic saccades (visually guided or reflexive) in PD patients (Chan et al., 2005, Hood et al., 2007, Chambers and Prescott, 2010), similar performance between PD patients and healthy individuals in a visually guided saccadic task, and inferior performance on a voluntary saccades task have been described (Briand et al., 1999).

Levodopa can improve the performance of PD patients on tests of voluntary saccades but not to the level of healthy individuals. Levodopa can also slow reaction time (saccadic latency) of reflexive saccades in PD patients but it does not improve hypometric saccades (Hood et al., 2007).

Saccades can be facilitated by the striatum via its inhibitory effect on the substantia nigra pars reticulata which results in liberation of the superior colliculus (SC); or supressed by its indirect effect of increasing tonic inhibition

via external globus pallidus or STN (Hikosaka et al., 2014). The eye movement abnormalities seen in PD can be explained in terms of excessive SC inhibition by the basal ganglia output nuclei and decreased activity of the basal ganglia-frontal cortex circuit (Terao et al., 2011). Supporting this theory, electrical stimulation of the substantia nigra pars reticulata can affect negatively both automatic and voluntary saccades in primates (Liu and Basso, 2008). Furthermore, DBS of the STN in PD patients has been shown to improve parameters of both memory and visually guided saccades (Yugeta et al., 2010).

The anti-saccades task is a relatively simple way to test an individual's own control over voluntary action. It consists of suppression of the urge to look to a target in the visual field and instead, look to the opposite direction of the target. Evidence from studies with primates and humans supports the notion that correct performance in the anti-saccades test requires top-down inhibition of saccade neurons in the SC and frontal eye field before the target appears (Munoz and Everling, 2004). This test has been used extensively to prove that voluntary saccades are affected in PD (Antoniades et al., 2015, Crevits et al., 2000, Briand et al., 1999, van Stockum et al., 2012, Hood et al., 2007).

Motor and reflection impulsivity, with jumping to conclusions and decisions, has been shown to occur in PD+ICB (Averbeck et al., 2014). The number of direction errors in the anti-saccades task has been positively correlated with impulsivity levels in healthy individuals (Spinella, 2004), but until the present date no studies assessing saccadic movements in patients with PD and ICBs have been published.

Automatic and voluntary saccades of PD+ICB were tested and compared to PD-ICB and healthy controls (HC). It was hypothesized that PD+ICB would make more premature saccades in both the pro and anti-saccades tasks and more frequent direction errors in the anti-saccades task.

4.2 Materials and methods

4.2.1 Study design and patient selection

Individuals with PD fulfilling the QSBB diagnostic criteria (Hughes et al., 1992) and active ICBs were recruited from PD clinics at the National Hospital for Neurology and Neurosurgery, Queen Square, London and matched by age, sex, PD duration and age at PD onset with PD patients without ICBs, and by age with healthy individuals recruited among relatives/spouses of PD patients. Patients with a diagnosis of Parkinson's disease dementia or with MoCA score of less than 26 were excluded. The research protocol was approved by the Queen Square Ethics Committee.

All participants were assessed with the MoCA and the FAB. Individuals with PD were also assessed with the QUIP-RS, the UPDRS part III and the AIMS. Diagnosis of ICBs was confirmed with a structured interview.

4.2.2 Saccadic assessment

To ensure PD patients were tested in the ON state, patients using levodopa were assessed one hour after intake. Eye movements assessments were conducted with an e(ye) BRAIN© T2 device. Details of the eyetracker setup can be seen in figure 6 on page 92. Before each task a twelve-point calibration of the eyetracker infrared cameras and automated calibration of the head sensor were conducted.

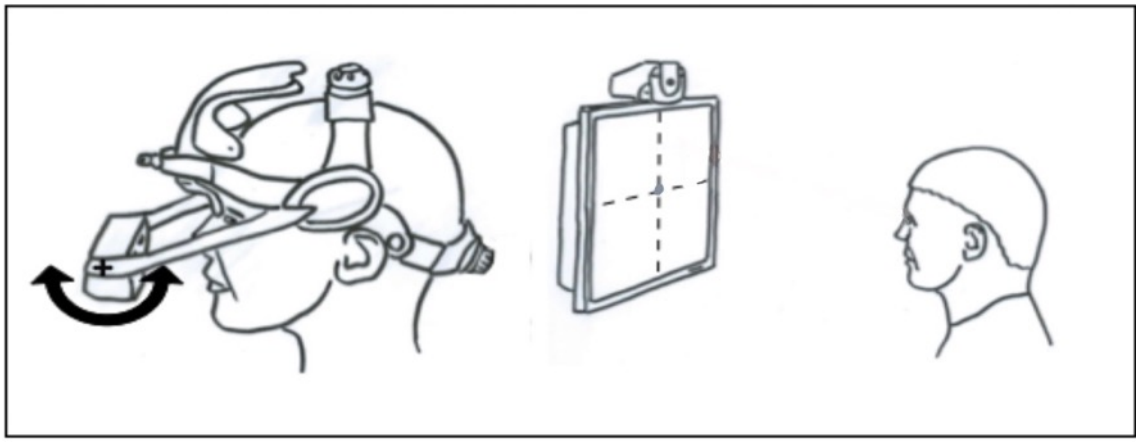


Figure 6. The e(ye)BRAIN T2 apparatus.

The helmet contains infrared cameras positioned below the line of sight to track pupils. The screen is maintained 60 cm away from the participant and head movements are tracked by another camera positioned on the top of the screen that detects light emitted by the helmet. Suricog™: e(ye)BRAIN T2 User's Manual, v 1.0 p16 and p29. Adapted image reproduced with permission from Suricog™.

Two research paradigms were created specifically for this research:

- **A pro-saccades task to test automatic saccades**.

Participants started by focusing on a grey dot measuring 0.32 degrees of visual angle on the centre of the screen. They were then instructed to make a saccade to a blue dot appearing eccentrically (15 degrees horizontally from centre) on the screen, displayed for 1500 milliseconds (ms). The central grey dot remained on display throughout the assessment. After 1500 ms, the blue dot disappeared, and patients had to return their eyes to the central fixation dot. Forty randomized trials were conducted to each side for each participant, totalling eighty trials. The 15 degrees amplitude was chosen based on previous publications showing normative values and that saccades to larger amplitudes are frequently inaccurate (Becker and Fuchs, 1969).

- **An anti-saccades task to test voluntary saccades**.

Participants were instructed to focus on a central grey dot measuring 0.32 degrees of visual angle that was displayed for 1500 ms. In this task a step paradigm was used, meaning that immediately after the grey dot disappeared, without delay, a red dot appeared randomly on either side of the screen 15 degrees horizontally away from the centre. Participants were instructed to look to the opposite side of the screen from the red dot and return their eyes to the central fixation point as soon as it reappeared, 1500 ms later. Forty randomized trials of the same amplitude (15 degrees) were conducted to each side for each participant, totalling eighty trials.

4.2.3 Statistical analysis

Data analysis was conducted initially with the e(ye)BRAIN software me(ye) analysis©. The computer was programmed to identify the first saccadic movement occurring after target onset that exceeded a speed of 30 degrees per second. The quality of the recording from both eyes was inspected visually and the channel with best recording chosen for data analysis. A poor-quality signal was identified when there was too much interference to prevent accurate

detection of saccades and/or when the computer failed to identify more than 75% of the expected saccadic movements, in both cases recordings were excluded from analysis.

All variables were exported to SPSS version 22 for data analysis. Data points outside the interquartile ranges were excluded from the analysis. All variables were tested for normality and statistical tests chosen accordingly. Due to the possibility that saccades with latency greater than 900 ms or lower than 120 ms were not related to stimulus presentation, these were excluded from the calculation of saccadic parameters. Considering that normal subjects generate a saccade within approximately 200 ms (Kveraga et al., 2002), saccades with latencies between 120 and 180 ms were classified as premature and included in the analysis. Latency and gain were calculated for each detected saccade and mean values used for comparison. The number of direction errors in the anti-saccades task was calculated for each participant and mean values used for comparison. A p value of less than 0.05 was considered significant.

4.3 Results

4.3.1 Demographic and clinical characteristics

There were 52 participants in the trial. Six patients with PD were excluded: two because of low MoCA scores, three because of poor quality of recording and one because of a technical fault with the computer processing unit. One healthy individual was excluded because of poor quality of the recording. Fifteen patients were included in each group: PD+ICB, PD-ICB and HC.

The groups were well matched for age but there was a higher proportion of females in the HC group. PD+ICB and PD-ICB had similar disease duration and age at PD onset. A similar proportion of PD patients were using DA and receiving a similar amount of dopaminergic treatment, measured as LEDD (Tomlinson et al., 2010). PD+ICB scored higher on the QUIP-RS, AIMS and UPDRS III. The scores on the MoCA and FAB did not differ between groups. Demographic and clinical data are detailed in table 16 on page 95.

Table 16. Demographic and clinical characteristics divided by group

	PD+ICB	PD-ICB	HC	p value
N	15	15	15	
Females (%)	2 (13.3)	3 (20)	8 (53.3)	**0.035***
Age (years)	53.6 (± 9.8)	54.6 (± 7.3)	53 (± 9.1)	0.880 ƒ
Average age at PD onset (years)	42.7 (± 10.3)	45.9 (± 7.5)	-	0.344†
Average PD duration (years)	11.1 (± 4.3)	8.7 (± 4.5)	-	0.152†
Hoehn & Yahr	2	1.8	-	0.057*
Current use of DA (%)	9 (60)	9 (60)		1.000*
Total DA LEDD (N = 9)	164.7 (± 133.3)	242.4 (± 96.6)	-	0.178†
Total LEDD	895.8 (± 397.5)	744.5 (± 466)	-	0.347†
QUIP-RS	39.9 (± 11.1)	10 (± 7.4)	-	**<0.001ƒ**
AIMS	7.4 (± 4.6)	2.8 (± 3.3)	-	**0.005 ƒ**
UPDRS III	24.6 (± 6.9)	13.7 (± 5.6)	-	**<0.001ƒ**
MoCA (median, IQR)	28 (27; 29)	29 (27; 30)	28 (27; 29.7)	0.533Ø
FAB (median, IQR)	17.5 (16; 18)	18 (17; 18)	18 (18; 18)	0.089 Ø

*Demographic and clinical characteristics divided by group. PD – Parkinson's disease. DA – dopamine agonist; LEDD – levodopa equivalent daily dose; QUIP-RS – Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale; UPDRS III – Unified Parkinson's Disease Rating Scale part III; AIMS – Abnormal Involuntary Movements Scale; MoCA – Montreal Cognitive Assessment; FAB – Frontal Assessment Battery; *Chi-square test; ƒ ANOVA; † Independent samples t-test; Ø Kruskal-Wallis test. Significant results in bold. Results expressed in mean values and standard deviation for variables with normal distribution or median values and interquartile range (IQR) for variables with non-normal distribution.*

In the PD+ICB group there were seven patients with singe ICBs (3 with CSB, 3 with punding and 1 with compulsive shopping) and eight with multiple ICBs (punding was present in 6 individuals, CSB in 5, compulsive eating in 4, compulsive shopping in 4 and pathological gambling in 1).

4.3.2 Pro-saccades task

The number of outlying data points excluded did not differ between groups as compared with the Kruskal-Wallis test in both the pro and anti-saccades tasks. Automatic saccades, tested with the pro-saccades task, did not differ between groups as displayed in table 17 on page 97.

4.3.3 Anti-saccades task

Voluntary saccades were assessed with the anti-saccades task. There was no difference in the number of premature saccades and saccadic latency between groups. Reaction time immediately after a direction error, however, was longer in PD+ICB.

Amplitude of anti-saccades differed between groups (table 18 on page 98), a post hoc analysis showed that PD+ICB made smaller amplitude saccades than HC ($p = 0.021$, Mann-Whitney U test). There was no difference between PD+ICB and PD-ICB ($p = 0.110$) and between PD-ICB and HC ($p = 0.097$).

The number of direction errors also differed between groups. A post hoc analysis revealed that PD+ICB made more direction errors than PD-ICB ($p = 0.006$) and HC ($p = 0.001$). The number of direction errors did not differ between PD-ICB and HC ($p = 0.802$). The anti-saccades test data is summarised in table 18.

Table 17. Pro-saccades task

	PD+ICB	PD-ICB	HC	p value
N	15	15	15	
Premature saccades (median, IQR)	9 (4; 13)	8 (2; 12)	7 (2; 10)	0.545*
Latency in ms (median, IQR)	299.9 (246.7; 316)	271.9 (246.2; 289.4)	264 (250.4; 302.5)	0.358*
Amplitude (°)	14.8 (± 2.2)	15.1 (± 2.6)	16.1 (± 2.3)	0.324**

*Comparison of the pro-saccades task results. Ms – milliseconds. *Kruskal-Wallis test; **ANOVA. Results expressed in mean values and standard deviation for variables with normal distribution or median values and interquartile range (IQR) for variables with non-normal distribution.*

Table 18. Anti-saccades task				
	PD+ICB	PD-ICB	HC	p value
N	15	15	15	
Premature saccades (median, IQR)	1 (0; 1)	0 (0; 2)	0 (0; 1)	0.310*
Latency in ms (median, IQR)	318.6 (308; 359)	300.2 (281; 378)	326.4 (285; 345)	0.315*
Latency after a direction error in ms (median, IQR)	377.8 (345; 440)	351 (312; 411)	356.4 (283; 415)	**0.05***
Amplitude in° (median, IQR)	13.5 (12; 15)	15.5 (13.8; 16.9)	16.8 (15.7; 18.5)	**0.035***
Direction errors (N)	31.1 (± 13.1)	18.9 (± 12)	15.2 (± 13.9)	**0.005****
Direction errors (%)	48.6 (± 22)	25.2 (± 16)	20.7 (± 19.5)	**0.001****

*Comparison of the anti-saccades task results. Ms – milliseconds. *Kruskal-Wallis test; **ANOVA. Significant results in bold. Results expressed in mean values and standard deviation for variables with normal distribution or median values and interquartile range (IQR) for variables with non-normal distribution.*

4.4 Discussion

This study is the first to assess saccadic eye movements of PD+ICB. Performance was similar between PD patients with and without ICBs and healthy controls in all parameters of the pro-saccades task, suggesting that automatic saccades are preserved in PD. While most, but not all, published studies have found preserved automatic saccades in individuals with PD (Briand et al., 1999, Chan et al., 2005, Hood et al., 2007, Chambers and Prescott, 2010) corroborating our findings, one study reported reduced amplitude of automatic saccades which was correlated with disease severity, measured by motor and cognitive impairment (Macaskill et al., 2012).

The SC is the point of convergence for cortical and subcortical structures that influence saccadic control (Munoz and Everling, 2004), and is modulated by the basal ganglia (Hikosaka et al., 2014). This structure in under tonic inhibition from the substantia nigra pars reticulata. Cortical visual signals are initially directed to the caudate, which connects to the nigra pars reticulata via direct and indirect pathways. The former inhibits the nigra and releases the SC to perform a saccade, whereas the latter increase the SC inhibition preventing the generation of saccades towards 'valueless objects' (Hikosaka et al., 2014, Kim et al., 2017). The nigra pars reticulata tends to be affected later in PD (Jellinger, 2011), therefore integrity of such pathways in the early stages of the disease could explain the preservation of pro-saccades.

It is interesting to note that more premature saccades were made in the pro-saccades task compared to the anti-saccades task. It has been shown that anticipatory saccadic movements can occur with predictable tasks, similar to our pro-saccades paradigm (Holmqvist et al., 2011).

Contradictory data on anti-saccadic reaction time in PD has been published, presumably relating to medication status and different paradigms (Briand et al., 1999). Here, all patients were tested during ON stage which may explain the lack of differences in anti-saccadic latencies between groups. The amplitude of anti-saccades, however, was lower in PD+ICB compared to HC. Previous reports have shown that PD patients without impulsivity have hypometric

saccades but here this finding was only replicated in PD+ICB (Briand et al., 1999), possibly due to the small sample size, as a trend for shorter saccades in PD-ICB compared to HC was identified. As previously described in a general PD population, saccadic hypometria of PD+ICB did not improve with levodopa (Hood et al., 2007).

PD+ICB exhibited longer anti-saccadic latencies immediately after a direction error. This could be explained by the fact that they were tested on medication as previous studies have shown that PD+ICB on dopaminergic treatment are more sensitive to negative feedback (Djamshidian et al., 2010, Djamshidian et al., 2012a).

Increased anti-saccadic error rate has been reported in drug naïve PD patients early in the course of the disease (Antoniades et al., 2015). The error rate found by Antoniades and colleagues in PD patients (15%) and controls (8.7%) (Antoniades et al., 2015) was less than the 25% and 20%, respectively, found in the present study. Considering that patients were assessed for 4 minutes in each task, without interruption, one has to consider the possibility that fatigue contributed to the higher error rate described here. However, another group has found higher error rates in healthy young adults (Li et al., 2012) than both Antoniades et al and the present study suggesting that PD-ICB and HC did not have an increased rate of anti-saccadic direction errors.

The similar error rate between PD-ICB and HC could be attributed to levodopa, as this medication has been shown to reduce anti-saccadic error rate in PD (Hood et al., 2007). The use of levodopa, however, was not enough to reduce the error rate of PD+ICB (nearly 50%). Patients with ICBs have a bias towards risky choices in decision making tasks (Djamshidian et al., 2010), reflection impulsivity (Djamshidian et al., 2012b) and temporal discounting (Milenkova et al., 2011). However, considering the short time between target onset and saccadic movement and the low number of premature saccades, it is unlikely that decision making abnormalities are responsible for the higher anti-saccadic error rate in PD+ICB. Previous studies show that correct performance in the anti-saccades task requires top-down inhibition of saccadic neurons in the SC before target onset (Munoz and Everling, 2004). PD-related dopaminergic

depletion in the dorsolateral prefrontal cortex coupled with deficits in cortical inhibitory circuits in PD+ICB (Djamshidian et al., 2011a) could be the mechanism behind the failure to suppress automatic saccades in individuals with ICBs (Pretegiani and Optican, 2017).

An important caveat is the higher UPDRS scores in PD+ICB, which could have contributed to an increase in the number of anti-saccadic direction errors. It has been described that anti-saccadic error rate and reaction time tend to increase as PD progresses (Terao et al., 2011, Kitagawa et al., 1994). However, there are important differences between the present study and previous research reporting saccadic abnormalities in advanced PD. Firstly, PD+ICB exhibited a very high error rate (48.62%), significantly higher than what has been described before by Kitagawa et al (36.2%). Secondly, the anti-saccadic reaction time reported here was shorter (318.6 ms) than what has been described previously (410 ms) (Kitagawa et al., 1994). Lastly, severity of bradykinesia has been correlated with longer anti-saccadic latencies (Kitagawa et al., 1994) but no differences in anti-saccadic latencies between PD+ICB and PD-ICB were found. Therefore, although the UPDRS III suggests that PD+ICB patients have more advanced PD, the findings from the anti-saccades task do not corroborate this. Although the UPDRS III motor score influences performance in PD-ICB (Kitagawa et al., 1994) it is likely that cognitive impulsivity is contributing to the poor performance in PD+ICB. Further studies with a larger sample size including patients with similar UPDRS III scores are needed to definitively answer this question.

One limitation of this study is the small sample size. This was addressed by sampling 80 saccades in each task, however this could have contributed to a lengthy testing procedure and fatigue that could have negatively affected performance of participants. To reduce fatigability, the eye movements assessment was conducted before the other tests and patients were offered breaks between tasks.

There were more female volunteers among HC. Previously published data suggests that saccadic velocity, accuracy and latency does not differ greatly between sexes (Wilson et al., 1993), although one study reported that women

tend to make more errors than men in the anti-saccades task (Li et al., 2012). However, the HC error rate of 20% is lower than the rates previously reported for both males and females.

4.5 Conclusion

This is the first study to assess saccadic parameters in patients with PD and ICBs. PD+ICB made hypometric voluntary saccades. Longer anti-saccades latencies after an error in PD+ICB suggest higher sensitivity to their negative performance. PD+ICB made a high number of direction errors in the anti-saccades task and this finding may have important clinical implications. If anti-saccadic error rate could be confirmed as a marker for ICBs in PD this could be used to inform choice of initial treatment in a particular individual. It may be appropriate that patients with early PD and a high rate of anti-saccades direction errors should avoid oral DA therapy and start treatment with low dose levodopa therapy.

Chapter 5: Dopamine dysregulation syndrome in Parkinson's disease is associated with lower alpha-synuclein load in the nucleus accumbens

5.1 Introduction

5.1.1 The dopaminergic reward pathway

The dopaminergic (or mesocorticolimbic) reward system consists of a series of structures located mainly in the midbrain and basal ganglia that attribute value to different stimuli in order to generate an appropriate behavioural response (figure 1). This system is of paramount importance to maintain an organism's homeostasis and the main neurotransmitter used is dopamine, albeit not the only one. Changes in the tonic release of dopamine from the ventral tegmental area in the midbrain to the NAc are the way the brain encodes the nature of a stimulus, with rewarding stimuli resulting in a fast and temporary increase and non-rewarding stimuli leading to the opposite, a sudden decrease in dopamine release (Damier, 2015). Stimuli that generate a sensation of pleasure or liking (hedonic response) are classified as rewarding. The hedonic response to sensory stimuli is facilitated by the NAc and the ventral pallidum through reciprocal connections. Within these structures there are areas rich in opioid receptors, called hedonic hotspots, that can amplify the hedonic response to sweet taste stimuli (Pecina et al., 2006, Smith and Berridge, 2007).

The NAc is also responsible for originating an appropriate behavioural response to different stimuli. Connections between this structure and other brain areas, like the amygdala and the prefrontal cortex, contribute to creating an association between stimulus and related events, facilitating future engagement (Kalivas and Volkow, 2005). Motivation to pursue determinate activity is modulated by the prefrontal cortex and the hippocampal subiculum via projections from the ventral striatum. Activation of the mesocorticolimbic pathway with consequent dopamine release results in two major simultaneous changes: stimulation of D1R will increase subiculum input keeping a subject focused on a task; and stimulation of D2R will inhibit the prefrontal cortex and

free the subject to engage with the task. Conversely, if a reward is not elicited dopamine levels drop removing the input from the subiculum and reducing prefrontal cortex inhibition, freeing the subject to shift task focus (figure 1) (Goto and Grace, 2005, Napier et al., 2015).

There are common brain areas that respond to rewards regardless of the type, supporting the idea of a general hedonic representation in the brain. These areas are the ventral striatum, anterior insula, anterior cingulate cortex and midbrain (Sescousse et al., 2010).

5.1.2 Structures implicated in impulsivity and drug abuse

In healthy individuals, impulsivity has been inversely correlated with D2R and D3R availability in the midbrain and positively correlated with the magnitude of amphetamine-induced dopamine release in the striatum (Buckholtz et al., 2010). Pathophysiological similarities between drug addiction and ICBs in PD suggest shared pathways between the two conditions. Evidence from imaging studies in drug addiction shows that large and rapid increases in extracellular dopamine may be the encoding mechanism through which dopamine attributes salience to an event in normal conditions. Therefore, dopaminergic drugs with fast brain uptake and clearance more closely mimic this natural process and tend to be more implicated in the experience of “high” and drug-induced reinforcement (Volkow et al., 2004). Recreational drugs have the ability to increase dopamine in the basal ganglia to a supra-physiological level, and this is believed to be an important step in the promotion of addiction (Wise and Rompre, 1989). With repeated drug use the hedonic response is lost in favour of habitual automatic responses (Everitt and Robbins, 2005).

In the molecular level, the transcription factor Delta-FosB has been shown to increase in the striatum after exposure to drugs of abuse and to enhance sensitivity to rewards in rats (McClung et al., 2004). PD patients with dyskinesias also have increased expression of this molecule in the posterior putamen suggesting its involvement in maladaptive neuroplasticity (Lindgren et al., 2011). Studies are needed to investigate whether similar changes are present in PD+ICB.

5.1.3 Parkinson's disease and Impulsive compulsive behaviours

A similar pattern of excessive release of dopamine in the ventral striatum to that described in drug abusers has been reported in PD+ICB. Using ^{11}C-Raclopride positron emission tomography (PET) in patients with PD, Evans and colleagues showed that individuals with DDS have enhanced dopamine release in the ventral striatum induced by levodopa (Evans et al., 2006). Similar changes in dopamine transmission also occur in non-substance addicted PD patients with other types of ICBs. O'Sullivan and colleagues demonstrated that medicated PD+ICB (including CSB, binge eating, punding, compulsive shopping, DDS, pathological gambling and reckless generosity) have increased dopamine release in the ventral striatum after exposure to reward-related cues. In that study, different ICBs elicited the same dopaminergic response providing further evidence to the theory that there is a general hedonic representation system in the brain (O'Sullivan et al., 2011).

In PD patients with pathological gambling, not only increased dopamine release in the ventral striatum has been demonstrated (Steeves et al., 2009), but these patients also exhibit hyperactivity of structures of the dopaminergic reward system. This suggests that pathological gambling in PD is a consequence of overstimulation of a relatively preserved mesocorticolimbic pathway (Cilia et al., 2008). However, a defective inhibitory network can also play a part, as PD patients with pathological gambling exhibit reduced blood flow to brain areas associated with response inhibition after receiving apomorphine (van Eimeren et al., 2010).

Structural abnormalities have also been described in PD+ICB, such as: cortical thinning in areas of the frontal cortex and corpus callosum, alongside volume reduction of the right NAc and volume increase of the amygdala (Biundo et al., 2015); volume loss in the NAc, caudate, hippocampus and amygdala, and increased thickening of anterior cingulate and frontal pole cortices, which could be attributed to either dopaminergic stimulation or a pre-existent vulnerability to addiction (Pellicano et al., 2015); and cortical thinning of the dorsolateral prefrontal and orbitofrontal areas in patients with punding (Yoo et al., 2015).

D3R are widely expressed in the limbic system of the human brain, particularly in cell cluster populations within the NAc (Suzuki et al., 1998) and have higher affinity for dopamine compared to D1R and D2R, making them more sensitive to changes in dopamine levels (Payer et al., 2014). It has been postulated that ICBs are a consequence of overstimulation of D3R by DA. Data supporting this connection comes mainly from observational clinical studies showing that the higher the selectivity of a dopamine agonist to D3R the greater the risk of ICBs as detailed in figure 2 (Seeman, 2015). Furthermore, tonic stimulation of dopamine receptors associated with the use of DA may impair negative feedback signalling by preventing drops in dopaminergic tonic stimulation, reducing negative reinforcement (van Eimeren et al., 2009). Despite previous findings that D3R expression is upregulated in drug addiction (Payer et al., 2014), in PD+ICB, no changes in D2R levels and no evidence of upregulation of D3R in the limbic striatum were found in a PET study (Payer et al., 2015).

Over the last decade our understanding of the pathophysiology of ICBs has markedly improved in parallel with increased scientific interest in this stimulating topic. Although data from animal models and imaging studies have shed some light on the associated structural and functional abnormalities encountered in PD patients with behavioural addictions, the cause of ICBs remains elusive. To the present date no post mortem study involving PD+ICB has been conducted. The QSBB has received donations from patients with PD who were troubled in life by DDS. This study was designed to identify cellular and molecular insights into the mechanisms of DDS that could translate into better clinical care and the development of novel pharmacological treatments.

5.2 Materials and methods

5.2.1 Study design and patient selection

Cases with pathologically proven PD who developed DDS in life were identified from the archives of the QSBB. Using the same database, cases with PD who had not exhibited ICBs matched by sex, age at PD onset, disease duration and

age at death were selected in a consecutive fashion, starting with more recent cases, to act as controls.

The medical records were systematically reviewed including primary and specialist care medical notes, correspondence between doctors and data collected from the QSBB prior to donation. Demographic and clinical data were collated, as well as information on ICBs and detailed medication history. Symptoms that were not mentioned in the notes were considered absent. Written consent for donation was obtained from all cases.

The decision to study the NAc was based on previous reports showing excessive dopaminergic release in the ventral striatum of PD+ICB (Evans et al., 2006, O'Sullivan et al., 2011) and a connection between excessive stimulation of D3R, which are mainly expressed in the NAc, and ICBs (Seeman, 2015). Two methods were selected based on the QSBB expertise and availability of antibodies with specific binding to the chosen targets: immunohistochemistry to analyse alpha-synuclein load and tyrosine hydroxylase (TH) levels; and western immunoblotting to quantify D2R and D3R protein levels. Additional western blotting to confirm alpha-synuclein levels was conducted. Additional brain regions were chosen to confirm whether any differences found were restricted to the NAc. For immunohistochemistry, the dorsal putamen and dorsal caudate were selected because these areas have not been implicated in the development of ICBs. For western blotting, one area with high levels of D2R and D3R (the dorsal putamen) and another with low levels (the inferior frontal cortex) were chosen (Luquin-Piudo and Sanz, 2011).

5.2.2 Sample preparation

Brain donations were processed according to QSBB standard operating procedures. After post-mortem, the brain was hemi-dissected and one half of the brain (usually the right) was frozen and stored at -80°C while the other half was fixed in 10% formalin for 3 weeks until neuropathological assessment. Paraffin-embedded blocks containing the anterior striatum including the NAc are routinely obtained during neuropathological examination of all PD cases donated to the QSBB. Initially, a case by case macroscopic review of the

paraffin-fixed blocks was conducted to confirm the presence of the NAc, putamen and caudate.

Subsequently, three 8 μm sections and one 12 μm section were cut and mounted on glass slides and left to dry in a 60°C oven over night. One 8 μm section was stained with haematoxylin and eosin and one 12 μm section with luxol fast blue according to QSBB standard operating procedures. After confirmation of adequate sampling of the NAc using microscopy, the remaining 8 μm sections were stained with alpha-synuclein and TH as described in the following section.

When flash frozen brain tissue was available, samples from the NAc, dorsal putamen and the frontal inferior gyrus were obtained by micro-dissection and prepared for western blotting as described later.

5.2.3 Immunohistochemistry

Eight μm sections were stained for TH and alpha-synuclein using similar immunohistochemistry techniques as described below.

Sample preparation

Initially, the samples were dewaxed using several changes of xylene of few minutes each. Sections were then washed in changes of 100% industrial methylated spirit (IMS) for several minutes each change and placed into a solution of hydrogen peroxide and methanol for 10 minutes at room temperature before being washed in running tap water for 10 minutes.

Antigen retrieval

Pre-treatment of the samples was conducted as follows: sections were treated in 98% formic acid for 10 minutes at room temperature and washed in running tap water for 10 minutes; sections were subsequently pressure cooked in the citrate buffer for 10 minutes and rinsed in running tap water and tris buffered saline (TBS); finally, sections were rinsed with de-ionised water and proteinase

K solution (Dako) was applied for 10 minutes at room temperature. Sections were transferred to TBS and placed into 10% powered milk solution for 30 minutes at room temperature.

Antibody solutions

The primary antibody was applied to the tissue section for one hour at room temperature and then rinsed off with TBS. This was followed by 3 five-minute washes in TBS. The secondary antibody was applied for 30 minutes at room temperature and then rinsed off in TBS. This was also followed by three five-minute washes in TBS. The ABC working solution was applied to all sections for 30 minutes at room temperature and rinsed off with TBS. This was followed by 3 five-minute washes, also in TBS. Sections were immersed in DAB solution (activated with the addition of hydrogen peroxide) for 5 minutes at room temperature. Subsequently, the sections were rinsed in TBS followed by running tap water for 10 minutes. Sections were then counterstained in Mayer's haematoxylin for 1 minute and washed in warm running tap water for 10 minutes before being dehydrated in ascending grade of IMS (70%, 90% and 100%), cleared in xylene and mounted.

Image analysis of alpha-synuclein and TH immunoreactivity

Digital images of TH and alpha-synuclein stained slides were captured using a high-resolution digital scanner (Leica SCN400). The NAc, putamen and caudate were extracted from the original image using Aperio ImageScope software (Leica Biosystems) and the obtained image processed with ImageJ software. To optimise the sampling of the regions of interest, a Bland-Altman plot (Bland and Altman, 1999) was used to identify the ideal number of random squares to be sampled from each brain region: 5 random squares of 1000 pixels each for the NAc and caudate, and 10 for the putamen. The threshold was adjusted to correctly identify the two-dimensional area of alpha-synuclein (Lewy bodies and neurites) and TH immunoreactivity. Aereal fraction was calculated as a ratio of immunostained pixels to the total number of pixels in the whole field and expressed as percentage. Mean values for the random squares were obtained and exported to SPSS 22 for statistical analysis. All the analysis was conducted

blinded to the presence of ICBs. To account for learning effect, all cases were analysed twice and only the second round of analysis was used for comparison.

The core and the shell of the NAc exhibit different immunoreactivity profiles. Considering that the core expresses calbindin and the shell calretinin immunoreactivity, an attempt to identify these structures was conducted using these two substances as markers. Despite previous reports showing good differentiation of these structures in humans using a selection of chemical markers (Prensa et al., 2003), clear boundaries between the shell and the core were not identified using only calbindin and calretinin.

Materials for immunohistochemistry

Reagents:

Citrate buffer

- 0.45g citric acid
- 5.8g tri-sodium citrate
- 2L deionised water

Tris-buffered saline (1x TBS)

- 10% 10x TBS in sterile deionized water (final formulation: 50mM Tris-Cl, pH 7.5, 150 mM NaCl)

ABC working solution

- Avidin/Biotin complex, for every 5 ml of TBS 2 drops of solution A and 2 drops of solution B were used

DAB solution

- 1 ml 5% DAB (3,3'-diaminobenzidine) in 100 ml TBS

Antibodies:

Primary and secondary antibodies are displayed in table 19 on page 111.

Table 19. Antibodies used for immunohistochemistry

Protein detected	Antibody name	Source	Species	Dilution
Primary antibodies				
Alpha-synuclein	Anti-alpha synuclein antibody Ab15530	Abcam	Rabbit polyclonal	1:1500
Tyrosine hydroxylase	Anti-tyrosine hydroxylase antibody Ab152	Sigma-Aldrich	Rabbit polyclonal	1:1000
Secondary antibody				
Rabbit IgG	Anti-rabbit IgG E0353	Dako	Swine	1:200 in TBS

Primary and secondary antibodies used for immunohistochemistry.

5.2.4 Western immunoblotting

As none of the commercially available D3R antibodies were suitable for immunohistochemistry, analysis of protein levels was conducted using Western immunoblotting. However, as western blot analysis requires flash frozen brain tissue, only 25 QSBB cases were available: 10 PD+ICB and 15 PD-ICB.

Protein preparation from brain tissue

Samples from the NAc, dorsal putamen and inferior frontal gyrus were obtained by micro-dissection performed by an experienced QSBB technician. Samples were stored at -80°C and maintained on dry ice prior to the homogenization. Frozen tissue samples were weighed and ice cold RIPA buffer (50 mM Tris-HCl, pH 8.0 containing 150 mM sodium chloride, 1.0% NP-40 or Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS (sodium dodecyl sulphate)) added at a 5:1 (v/v) ratio of buffer to tissue. The RIPA buffer was supplemented with 1% protease inhibitor cocktail and phosphatase inhibitor (both Sigma-Aldrich). Subsequently, 500 µL of RIPA buffer was added to each. Samples were then homogenized with a Qiagen Tissueruptor homogeniser. Homogenates were centrifuged in a microcentrifuge for 20 minutes at 12000 rpm at 4°C. Lastly, the supernatants were collected and stored at -80°C.

Protein concentration determination

Due to variable protein concentrations of brain tissue homogenates, protein concentrations were determined using the BioRad DC Protein Assay. This ensured that equal amounts of protein per sample were loaded into each well of SDS-polyacrylamide gels for electrophoretic separation prior to immunoblotting. A quantification of sample protein was made using a standard curve derived from known concentrations of bovine serum albumin (BSA).

Using a 2.0 mg/mL solution of BSA, a set of 800µL standard dilutions were made in deionized water with a range of 0 to 150 µg/mL. Samples were diluted 1:25 by mixing 1 µL with 24 µL of deionized water. Five µl of standards and brain samples were pipetted in triplicate into individual wells of a 96-well plate.

Twenty-five µl of Reagent A were added into each well. Next, 200 µl of Reagent B were added into each well, mixed and incubated at room temperature for 10 minutes. Absorbance at 750 nm was measured using the Tecan Spark 10M plate reader. The absorbance values for the BSA standards were plotted on a graph using Microsoft Excel, and the formula for a straight line was determined using the linear section of the graph (normally 0 to 150 µg/mL). This formula and the dilution factor were then used to calculate the concentration of the protein samples using their absorbance values.

Western immunoblot analysis of proteins

Immunoblot analysis of proteins is a routine method used for studying complex protein mixtures. Firstly, the proteins are separated according to molecular weight using SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Laemmli, 1970) followed by immobilisation by transfer to a nitrocellulose membrane and detection of specific proteins by antibodies.

Equal masses of protein samples were prepared by mixing with 10% v/v reducing agent (Invitrogen) and 6x loading dye (BioRad Criterion) and denaturated at 100°C for 10 minutes. For SDS-PAGE, the BioRad Criterion system was used, which comprises pre-cast Bis-Tris polyacrylamide 4-12% gradient gels. Thirty µL samples were loaded into the wells of the gel alongside 5 µL of SeeBlue (Invitrogen) pre-stained protein size markers. Electrophoresis was performed in running buffer containing 3-(N-morpholino) propanesulphonic acid (MOPS) at 200 V until the dye front reached the bottom of the gel, normally within 50 minutes in MOPS buffer. The apparatus was then disassembled, and the separated proteins were transferred to a nitrocellulose membrane using the semi-dry Trans-Blot Turbo machine (BioRad). Briefly, this entails the 200 V electrophoresis for 10 minutes of the protein from the gel onto the membrane in semi-dry transfer buffer.

Excess protein binding sites of the membranes were blocked by incubation for 1 hour with 5% BSA (Sigma-Aldrich) in TBS. Primary antibodies against the proteins of interest were diluted at defined rations in TBS containing 0.05% (v/v) Tween-20 (TBSt) and incubated with the membranes for a defined period.

Typically, this was overnight incubation at 4°C. Membranes were then washed with TBSt, firstly, followed by 3 x 10-minute washes with shaking. The membrane was then incubated for 1 hour at room temperature with secondary fluorescently-labelled detection antibody (Li-Cor) against the primary antibody diluted 1:20000 in TBSt. This was followed by two washes with TBSt and a final wash in TBS. Membranes were scanned on a Li-Cor Odyssey 3000 for fluorescence detection of immunolabelled protein bands.

Densitometry of immunoblots

Considering the total number of samples, two gels were required for each comparison. To allow statistical comparison between gels, clinical data was used to choose an optimal control that was included in every gel (internal control). Immunoblot scans were analysed by densitometry using Image Studio Lite software (Li-Cor). A region of interest (ROI) was drawn around the largest/brightest band, and ROIs of the same dimensions drawn around protein bands for all other samples to be quantified. Mean intensities of each ROI were then analysed in Microsoft Excel. In order to calculate net band intensity, background readings were subtracted from band intensity readings. Signal intensity values of each band were normalised for beta-actin and, subsequently, for the optimal internal control. All comparisons were run three times and mean values used for statistical analysis. Immunoblot results were expressed as proportional/fold change in intensity between cases and controls.

Materials for western blotting

<u>Reagents:</u>

Radioimmunoprecipitation (RIPA) buffer

- 150 mM NaCl (Sigma-Aldrich)
- 5 mM EDTA, pH 8.0 (Life technologies)
- 50 mM Tris-HCL, pH 8.0 (Sigma-Aldrich)
- 1 mL 1.0% NP-40 (IGEPAL CA-630)
- 5 mL 0.5% 10% sodium deoxycholate (Sigma-Aldrich)
- 1 mL 1.0% 10% SDS (Sigma-Aldrich)
- 84 mL dH20

- 1x complete mini protease inhibitor cocktail (Sigma-Aldrich)
- 1x PhosSTOP phosphatase inhibitor cocktail (Sigma-Aldrich)

Running buffer

- 100 mL 20x MOPS (BioRad)
- 1900 mL ultra-pure water

Tris buffered saline (1X TBS)

- 10% 10x TBS on sterile deionized water

Blocking buffer

- 5 g BSA (Sigma-Aldrich)
- 100 mL 1x TBS

TBSt

- TBS supplemented with 0.1% vol/vol Tween 20 (Sigma-Aldrich)

Antibodies:

Primary and secondary antibodies are displayed in table 20 on page116.

Table 20. Antibodies used for western immunoblotting

Protein detected	Antibody name	Source	Species	Dilution
Primary antibodies				
Dopamine D2 receptor	ab85367	Abcam	Rabbit polyclonal	1:100
Dopamine D3 receptor	EPR10148	Abcam	Rabbit monoclonal	1:100
Beta-Actin	A2228	Sigma-Aldrich	Mouse monoclonal	1:1000
Alpha-synuclein	610787	BD Biosciences	Mouse monoclonal	250 µg/mL
Secondary antibodies				
Rabbit IgG	IRDye 800 CW	Li-Cor	Donkey	1 µg/mL
Mouse IgG	IRDye 680 RD	Li-Cor	Donkey	1 µg/mL

Primary and secondary antibodies used for western blotting.

5.2.5 Lewy pathology and Alzheimer's disease neuropathological changes analysis

All cases were quantified for Lewy pathology and Alzheimer's disease neuropathological changes. PD pathology was investigated using the Braak staging system, which is able to determine disease progression by assessing the presence of Lewy pathology in different structures of the central nervous system: the lower brain stem (stage 1), pontine nuclei (stage 2), midbrain (stage 3), basal prosencephalon and mesocortex (stage 4), neocortex (stage 5), and primary areas of the neocortex (stage 6) (Braak et al., 2003). Cortical Lewy pathology was quantified with the McKeith criteria, whereby a semi-quantitative analysis of the presence of Lewy bodies in five regions of the cortex (transentorhinal, cingulate, temporal, frontal and parietal) is used to classify each case as brain-stem predominant, limbic (transitional) or neocortical (McKeith et al., 1996).

Alzheimer's disease pathology was also quantified. The Braak and Braak staging system was used to compute tau neurofibrillary deposits. This staging system assesses the spread of neurofibrillary tangles and neuropil threads through cortical areas: the transentorhinal cortex (stages I and II), limbic areas (stages III and IV) and isocortical areas (stages V and VI) (Braak and Braak, 1991). Amyloid beta was accounted for with the Thal staging of amyloid beta deposition, which assesses the evolution of amyloid beta deposition in the brain in five stages. Stage 1 is characterized by involvement of the neocortex, stage 2 allocortex, stage 3 diencephalic nuclei, stage 4 brainstem nuclei and stage 5 the cerebellum (Thal et al., 2002).

We have also used the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score (Mirra et al., 1991), a semi-quantitative measure of neuritic plaques that takes into account patients' age and plaque frequency in the most affected neocortical area to give a probability of Alzheimer's disease diagnosis; and The National Institute of Aging-Alzheimer's Association (NIA-AA) score. The latter assesses beta amyloid plaques, neurofibrillary tangles and neuritic plaques to identify one of four levels of Alzheimer's disease neuropathological changes: not, low, intermediate or high (Hyman et al., 2012).

5.2.6 Statistical analysis

All variables were tested for normality. Parametric data was analysed using independent samples t-test and non-parametric data Mann-Whitney U and Wilcoxon matched pairs. Mann-Whitney U test was used for all variables obtained from western blotting. Proportions were compared with the Pearson chi-square test, except if the minimum expected cell count was less than five, when the Fisher's exact test was used. A p-value of less than 0.05 was considered significant. Data was analysed using SPSS 22.

5.3 Results

5.3.1 Clinical and demographic data

Twenty-three PD+DDS were identified from the QSBB archives and matched by sex, age at PD onset, age at death and PD duration with thirty PD-ICB. All patients had been assessed by specialists throughout disease course. One patient in the control group had DDS, therefore 24 patients were included in the PD+DDS group and 29 in the control group (PD-ICB). Among PD+DDS, ten individuals (41.6%) had multiple behavioural addictions. Details on the types of ICBs can be seen in table 21 on page 119.

The most common cause of death was pneumonia (8 PD+DDS and 12 PD-ICB), followed by end stage PD (5 PD+DDS and 7 PD-ICB) and septicaemia (3 PD+DDS and 5 PD-ICB). Causes of death according to group are displayed in table 22 on page 120.

Table 21. Types of impulsive compulsive behaviours

N	ICBs
16	Isolated DDS
2	DDS and CSB
1	DDS and punding
1	DDS and pathological gambling
2	DDS, CSB and compulsive shopping
1	DDS, CSB and punding
1	DDS, CSB, compulsive eating and punding

The different types of ICBs diagnosed in the study population. ICBs – impulsive compulsive behaviours; DDS – dopamine dysregulation syndrome; CSB – compulsive sexual behaviour.

Table 22. Causes of death divided by group

	PD+DDS (N = 24)	PD-ICB (N =29)
Pneumonia	8	12
Parkinson's disease	5	7
Septicaemia	3	5
Ischaemic heart disease	1	1
Heart failure	2	0
Respiratory failure	1	0
Pulmonary embolism	1	0
Asthma attack	1	0
Malnutrition	1	0
Dissecting aortic aneurysm	1	0
Sudden death	0	1
Metastatic carcinoma	0	1
Aortic aneurysm	0	1
Urinary tract infection	0	1

Causes of death separated by group. PD+DDS – Patients with Parkinson's disease and dopamine dysregulation syndrome; PD-ICB – Patients with Parkinson's disease without impulsive compulsive behaviours.

The proportion of males, age at PD onset, PD duration, age at death and prevalence of dyskinesias did not differ between groups (table 23 on page 122). A similar proportion of patients used DA anytime during disease progression and a non-significant higher proportion of PD+DDS were using DA at death. There was a trend for higher DA peak dose, measured in LEDD as previously described (Tomlinson et al., 2010). Duration of DA use, DA end dose and proportion of patients using MAOi anytime during disease course did not differ between groups. Lifetime cumulative dose of levodopa was calculated as described elsewhere (Parkkinen et al., 2011) and was statistically similar between groups. The dose of all PD medications at death was calculated in LEDD revealing that PD+DDS used more medication than controls.

5.3.2 Alpha-synuclein

Alpha-synuclein pathology was initially identified by immunohistochemistry. One NAc sample from a patient with DDS was damaged and removed from data analysis. Dorsal caudate from 21 PD+DDS and 27 controls were available for analysis, as well as dorsal putamen from 22 PD+DDS and 29 controls. Lewy bodies and neurites were seen in all three regions as displayed in figure 7 on page 123.

Aereal fraction analysis revealed significant differences in the NAc analysis, with PD+DDS showing lower alpha-synuclein load compared to PD-ICB. No differences were seen between groups in the putamen and caudate. Total alpha-synuclein load was calculated as the sum of alpha-synuclein stained area from all three structures and was non-significantly lower in the PD+DDS group (table 24 on page 124 and figure 8 on page 125).

Table 23. Demographic and clinical data

	PD+DDS	PD-ICB	p value
Male sex	79.2%	75.8%	0.775*
Age at PD onset (years)	50 (± 10)	51.8 (± 5)	0.480‡
PD duration (years)	20.6 (± 5.5)	21.4 (± 3.6)	0.481Þ
Age at death (years)	70.5 (± 9.4)	73.2 (± 4.7)	0.342‡
Dyskinesias (%)	95.8%	75.8%	0.059§
LEDD at death	1202.6 (± 653.2)	777.3 (± 448.5)	**0.007**Þ
Levodopa lifetime cumulative dose (kg)	5301.5 (± 4221)	3475.1 (± 2651)	0.077‡
DA use anytime (%)	91.3%	86.2%	0.682§
DA at death (%)	45.8%	34.4%	0.400*
DA peak dose in LEDD	623.5 (± 644)	317.6 (± 255)	0.050‡
	N = 21	N = 25	
DA end dose in LEDD	213.14 (± 234)	173.8 (± 105)	0.057‡
	N = 11	N = 18	
DA duration (years)	8.65 (± 5.6)	6.91 (± 5.5)	0.360‡
MAOi anytime (%)	79.2%	89.6%	0.444§

*Comparison of demographic and clinical data. PD – Parkinson's disease;; PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs; LEDD – levodopa equivalent daily dose; DA – dopamine agonists; MAOi – monoamine oxidase inhibitors. Results expressed in mean values and standard deviation or proportions. Significant results in bold. *Chi-square; ‡ Mann-Whitney U test; Þ Independent samples t-test; § Fisher's exact test.*

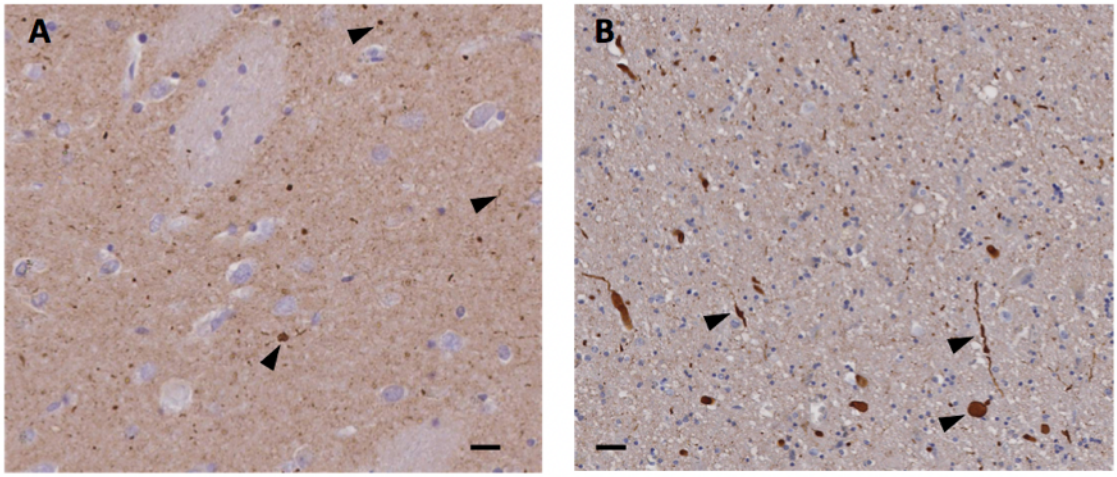


Figure 7. Lewy pathology.

Lewy bodies and neurites (black arrows) were seen in the dorsal putamen (panel A), the nucleus accumbens (panel B) and the dorsal caudate. Anti-alpha synuclein antibody manufactured by Abcam (Ab15530). On the left scale bar represents 50 μm and on the right 25 μm.

Table 24. Alpha-synuclein quantification by aereal fraction analysis			
	PD+DDS (N = 24)	PD-ICB (N = 29)	p value
Nucleus accumbens	0.0828 (0.099) N = 23	0.2330 (0.406) N = 29	**0.006***
Caudate	0.0526 (0.169) N = 21	0.1108 (0.217) N = 27	0.066*
Putamen	0.1276 (0.276) N = 22	0.1343 (0.210) N = 29	0.669*
Total alpha-synuclein load	0.4069 (0.558)	0.6022 (0.616)	0.072*

*Alpha-synuclein quantified by aereal fraction analysis. PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs. Results expressed in median values and interquartile ranges. Significant results in bold. *Mann-Whitney U test.*

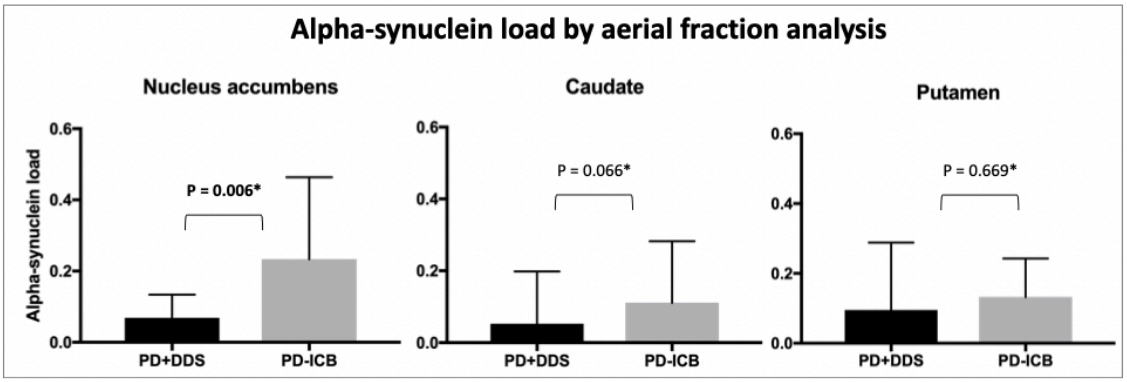


Figure 8. Quantification of alpha-synuclein load by aereal fraction analysis.

*Lower alpha-synuclein load was detected in the nucleus accumbens (NAc) of PD+DDS. No differences were seen in the caudate and putamen. The y axis represents the ratio of immune-stained pixels to the total number of pixels in the whole field expressed as percentage. PD+DDS – patients with PD and DDS; PD-ICB – patients with PD without ICBs. Results expressed in median and interquartile ranges. Significant results in bold. *Mann-Whitney U test.*

A comparison of alpha-synuclein load between the three regions was conducted. When all cases were assessed together no differences were found as seen in figure 9 on page 127 (Friedman test; p = 0.646). A post hoc analysis revealed that PD-ICB had higher levels of alpha-synuclein in the NAc compared to the putamen (Wilcoxon matched pairs; p = 0.002) and the caudate (Wilcoxon matched pairs; p 0.039).

Western blot analysis of alpha-synuclein confirmed the finding obtained by immunohistochemistry. Samples from 10 PD+DDS and 15 PD-ICB cases were available for comparison. Alpha-synuclein was identified as a single band immediately above the 17 KDa marker as displayed in figure 10 on page 128 (predicted molecular weight 19 KDa). Comparison between groups revealed that alpha-synuclein levels in the NAc of PD+DDS were 79% of PD-ICB, significantly lower. Alpha-synuclein levels of PD+DDS were 110% of PD-ICB in the frontal cortex and 107% of PD-DDS in the dorsal putamen, which did not reach statistical significance (Table 25 on page 129 and figure 11 on page 130).

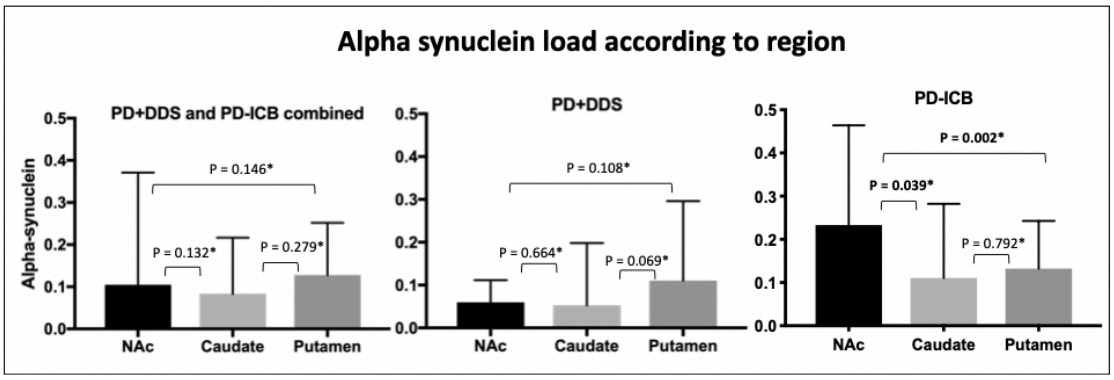


Figure 9. Comparison of alpha-synuclein load in different structures.

*There were no differences in alpha-synuclein levels between the studied brain regions in PD+DDS and when all cases were analysed together. PD-ICB exhibited higher alpha-synuclein load in the NAc compared to the caudate and the putamen. The y axis represents the ratio of immune-stained pixels to the total number of pixels in the whole field expressed as percentage. PD+DDS – patients with PD and DDS; PD-ICB – patients with PD without ICBs; NAc – nucleus accumbens. Results expressed in median and interquartile ranges. Significant results in bold. *Wilcoxon matched pairs.*

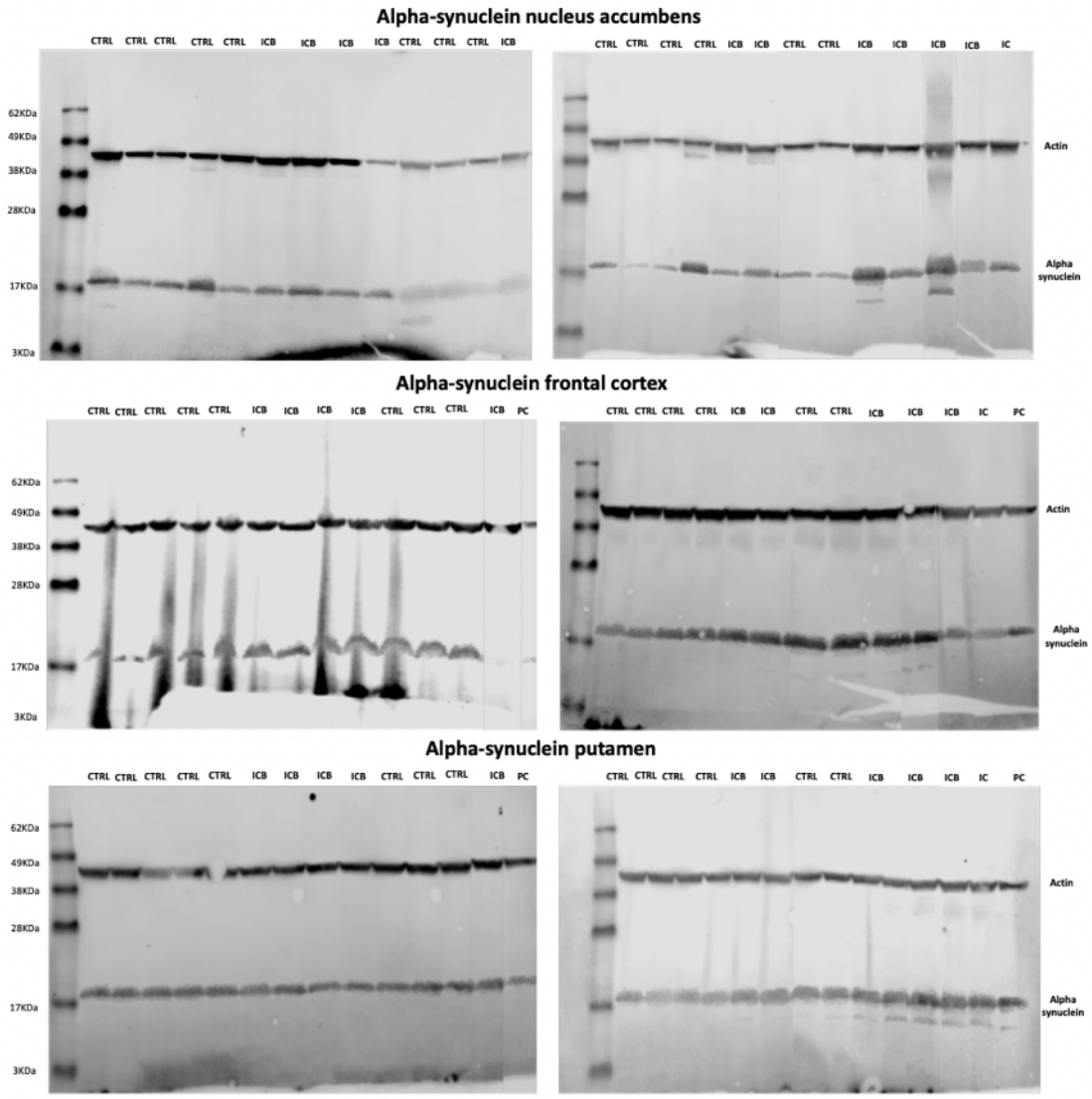


Figure 10. Alpha-synuclein immunoblotting of the nucleus accumbens (NAc), inferior frontal cortex and dorsal putamen.

Alpha-synuclein was identified as a single band immediately above the 17 KDa marker (predicted molecular weight 19 KDa). Two gels were required for each comparison and an internal control (without ICBs) was used to allow comparison between gels. PD+DDS had lower alpha-synuclein load in the NAc, no differences were seen in the other brain regions. ICB – patients with Parkinson's disease and dopamine dysregulation syndrome; CTRL – Patients with Parkinson's disease without impulsive compulsive behaviours; IC – internal control; PC – positive control.

Table 25. Alpha-synuclein quantification by western immunoblotting			
	PD+DDS (N = 10)	PD-ICB (N = 15)	p value
Nucleus accumbens	0.9244 (0.527)	1.1673 (0.679)	**0.031***
Frontal cortex	0.7177 (0.488)	0.6550 (0.310)	0.496*
Putamen	1.416 (0.486)	1.324 (0.450)	0.531*

*Alpha-synuclein assessed by western immunoblotting. PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs. Results expressed in median values and interquartile ranges. Significant results in bold. *Mann-Whitney U test.*

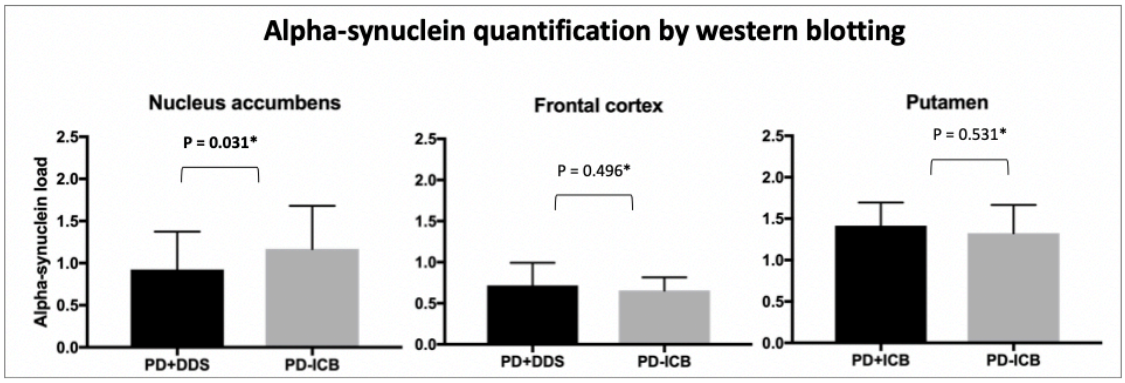


Figure 11. Quantification of alpha-synuclein by western immunoblotting.

*Lower alpha-synuclein load was seen in the nucleus accumbens in the PD+DDS group, corroborating the immunohistochemistry analysis. The y axis represents signal intensity normalised for beta-acting and for the optimal internal control. PD+DDS – patients with PD and DDS; PD-ICB – patients with PD without ICBs. Results expressed in median and interquartile ranges. Significant results in bold. *Mann-Whitney U test.*

5.3.3 Tyrosine hydroxylase

Similar to the alpha-synuclein analysis, one NAc sample from a patient with DDS had been damaged and was removed from data analysis. Caudate samples from 21 PD+DDS and 27 PD-ICBs and putamen from 22 cases and 29 controls were available for comparison. Quantification of TH immunoreactivity showed similar TH levels in both groups and in all three structures as displayed in table 26 on page 132 and figure 12 on page 133. Total TH level, calculated as the sum of TH levels from all three regions, was also similar between PD+DDS and PD-ICB.

A comparison of TH immunoreactivity in the different brain regions was conducted. When all cases were analysed together TH levels were significantly different (Friedman test; $p < 0.001$), revealing a gradient of staining between the three structures as displayed in figure 13 on page 134. Post hoc analysis revealed higher TH levels in the NAc compared to the caudate (Wilcoxon matched pairs; $p < 0.001$) and in the caudate compared to the putamen (Wilcoxon matched pairs; $p < 0.001$) (figure 14 on page 135). The same findings were obtained when the analysis was conducted within groups.

Table 26. Tyrosine hydroxylase quantification by aereal fraction analysis

	PD+DDS (N = 24)	PD-ICB (N = 29)	p value
Nucleus accumbens	12.98 (14.98) N=23	12.18 (11.32)	0.949*
Caudate	4.04 (7.02) N = 21	3.80 (8.21) N = 27	0.484*
Putamen	1.53 (3.02) N = 22	1.00 (1.45) N=29	0.250*
Total TH	18.94 (27.47)	17.87 (24.39)	0.665*

*Tyrosine hydroxylase levels assessed by aereal fraction analysis. PD+DDS – patients with Parkinson's disease and dopamine dysregulation syndrome; PD-ICB – Parkinson's disease patients without impulsive compulsive behaviours. Results expressed in median values and interquartile ranges. *Mann-Whitney U test.*

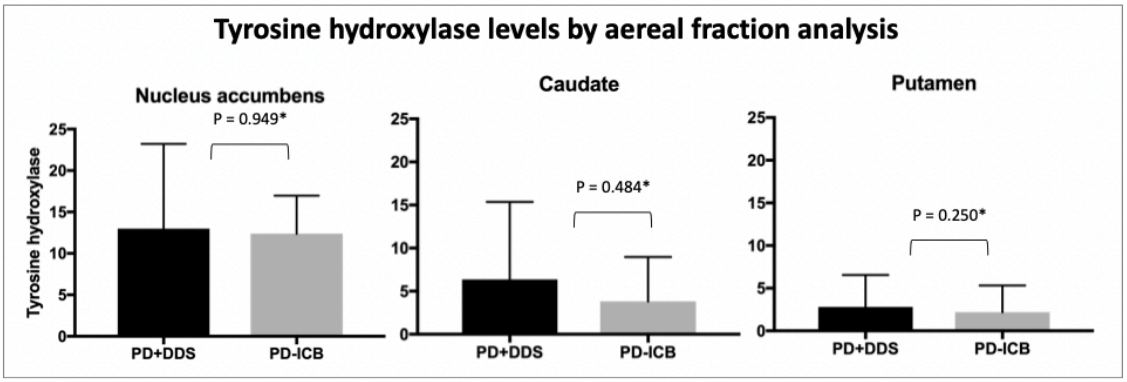


Figure 12. Quantification of tyrosine hydroxylase levels by aereal fraction analysis.

*Similar levels of TH were seen in all three brain regions. The y axis represents the ratio of immune-stained pixels to the total number of pixels in the whole field expressed as percentage. PD+DDS – patients with Parkinson's disease and dopamine dysregulation syndrome; PD-ICB – patients with Parkinson's disease without impulsive compulsive behaviours. Results expressed in median and interquartile ranges. *Mann-Whitney U test.*

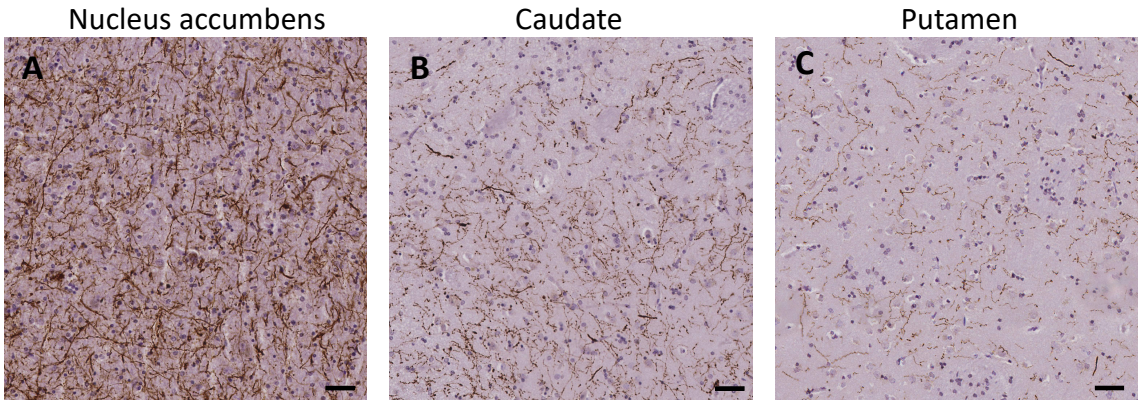


Figure 13. Tyrosine hydroxylase staining in different regions.

A - nucleus accumbens (NAc); B – dorsal caudate; C – dorsal putamen. TH immunoreactivity was higher in the NAc, followed by the caudate and the putamen with no differences between patients with and without dopamine dysregulation syndrome. Anti-tyrosine hydroxylase antibody manufactured by Sigma-Aldrich (Ab152). Scale bar represents 50 μm.

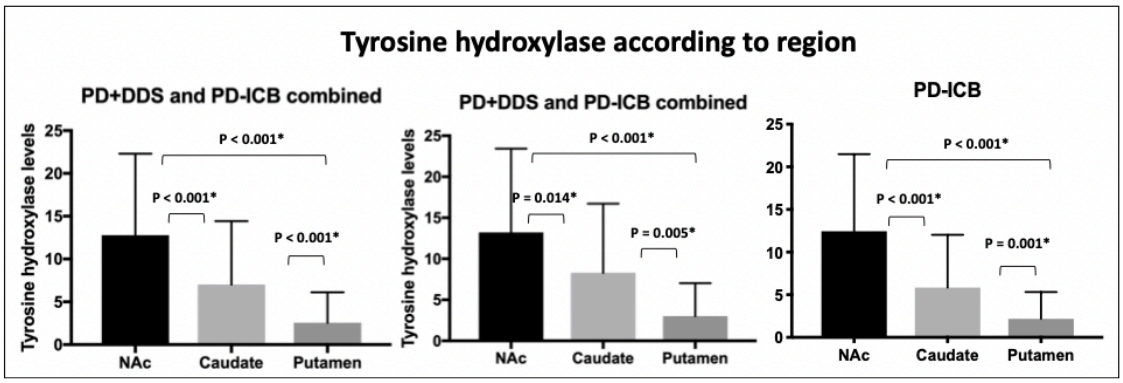


Figure 14. Comparison of tyrosine hydroxylase levels in different regions.

*Higher TH levels were seen in the NAc, followed by the caudate and the putamen. Similar results were achieved when cases were analysed separately, according to the presence of ICBs. The y axis represents the ratio of immune-stained pixels to the total number of pixels in the whole field expressed as percentage. NAc – nucleus accumbens. Results expressed in median and interquartile ranges. Significant results in bold. *Wilcoxon matched pairs.*

5.3.4 Dopamine D2 and D3 receptors

Frozen tissue samples from 10 PD+DDS and 15 PD-ICB were available. The expected molecular weight of D2R is 49 KDa. Immunoblot analysis of D2R revealed a single band of 49 KDa of molecular weight as displayed in figure 15 on page 137.

D2R levels of PD+DDS were 81% of PD-ICB in the NAc, 92% in the frontal cortex and 96% in the putamen but the differences did not reach statistical significance as seen in table 27 on page 138 and figure 16 on page 139.

D3R predicted molecular weight is 44 KDa. Immunoblot analysis of D3R revealed a single band immediately below the 49 KDa marker as detailed in figure 17 on page 140.

Table 28 on page 141 and figure 18 on page 142 shows D3R levels in different brain regions separated by groups. Signal intensity of PD+DDS was 66% of PD-ICB in the NAc, 102% in the frontal cortex and 118% in the dorsal putamen. Lower D3R levels were detected in the NAc of PD+DDS, but the difference did not reach statistical significance.

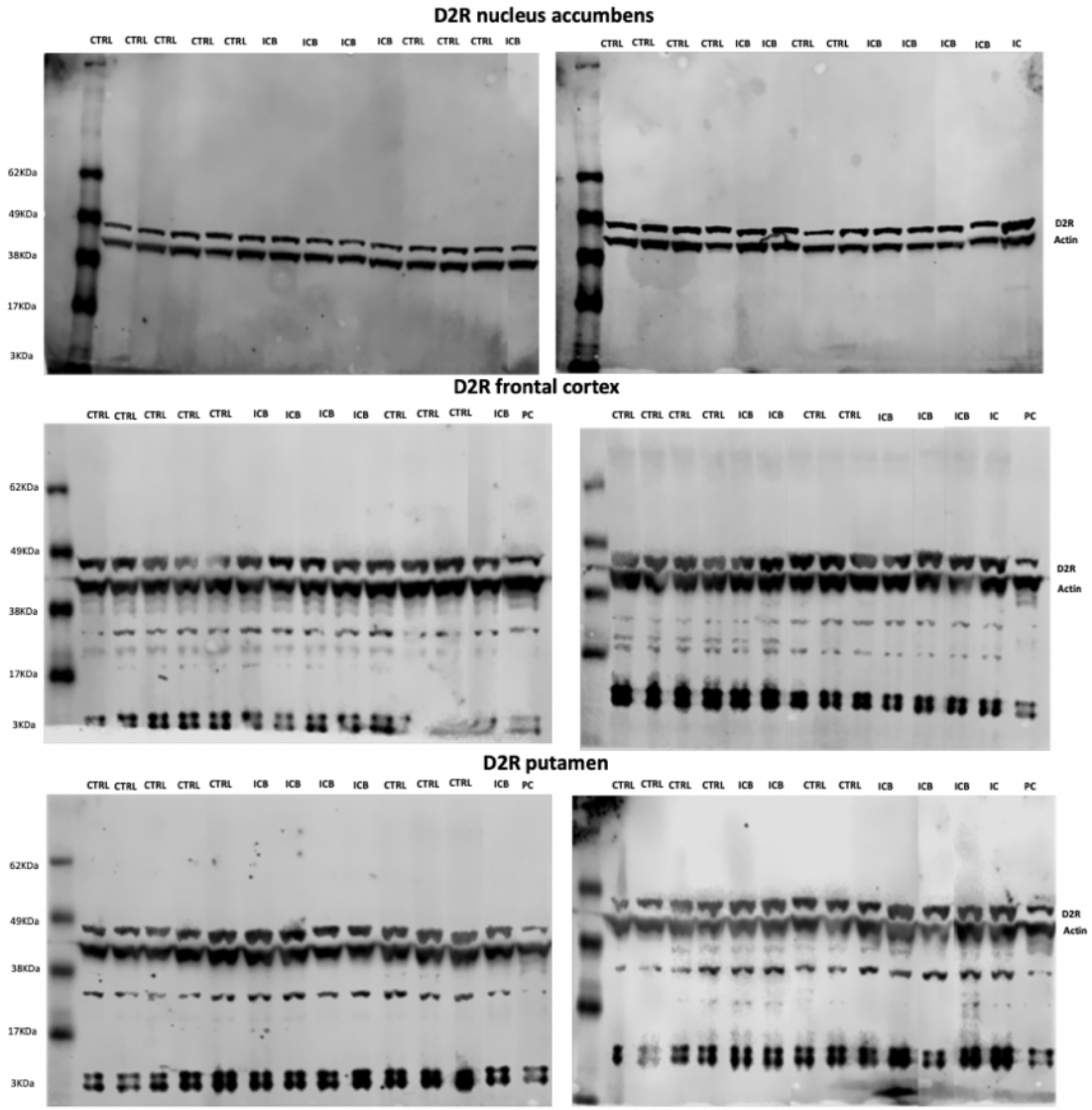


Figure 15. Dopamine D2 receptor (D2R) immunoblotting of the nucleus accumbens (NAc), inferior frontal cortex and dorsal putamen.

D2R identified as a single band with 49 KDa of molecular weight. Two gels were required for each comparison, an internal control (without ICBs) was used to allow comparison between gels. No differences in D2R protein levels were seen. ICB – patients with Parkinson's disease and dopamine dysregulation syndrome; CTRL – Patients with Parkinson's disease without impulsive compulsive behaviours; IC – internal control; PC – positive control.

Table 27. Dopamine D2 receptor protein levels

	PD+DDS (N = 10)	PD-ICB (N = 15)	p value
Nucleus accumbens	1.23 (1.51)	1.52 (1.63)	0.395*
Frontal cortex	0.99 (0.22)	1.07 (0.28)	0.428*
Putamen	0.96 (0.48)	1.00 (0.49)	0.567*

*Dopamine D2 receptor signal intensity assessed by western immunoblotting. D2R levels of PD+DDS were lower in the NAc, but the difference did not reach significance. PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs. Results expressed in median values and interquartile ranges. *Mann-Whitney U test.*

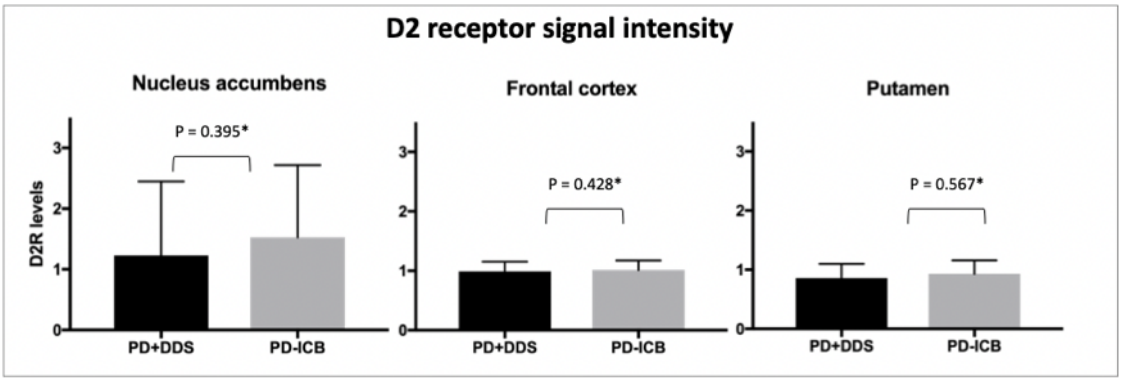


Figure 16. Comparison of D2 receptor (D2R) signal intensity between PD patients with DDS (PD+DDS) and PD controls (PD-ICB).

*No significant differences were found in D2R levels. The y axis represents signal intensity normalised for beta-acting and for the optimal internal control. Results expressed in median and interquartile ranges. No significant differences were seen. *Mann-Whitney U test.*

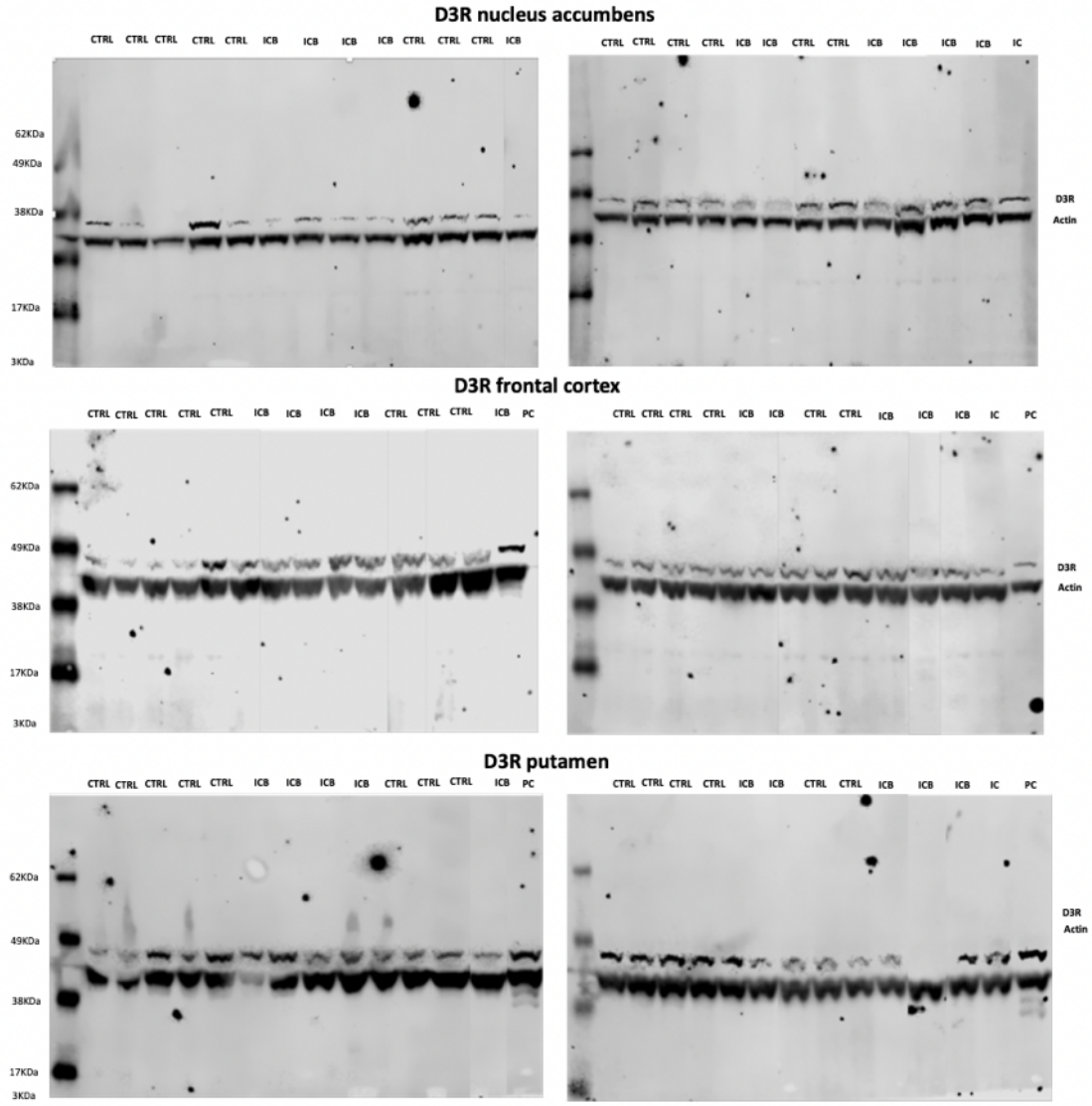


Figure 17. Dopamine D3 receptor (D3R) immunoblotting of the nucleus accumbens (NAc), inferior frontal cortex and dorsal putamen.

D3R identified as a single band immediately below the 49 KDa marker (expected molecular weight of 44 KDa). Two gels were required for each comparison, an internal control (without ICBs) was used to allow comparison between gels. No differences were seen. ICB – patients with Parkinson's disease dopamine dysregulation syndrome; CTRL – Patients with Parkinson's disease without impulsive compulsive behaviours; IC – internal control; PC – positive control.

Table 28. Dopamine D3 receptor protein levels

	PD+DDS (N = 10)	PD-ICB (N = 15)	p value
Nucleus accumbens	0.669 (0.77)	1.000 (0.48)	0.091*
Frontal cortex	1.238 (0.62)	1.204 (0.56)	0.683*
Putamen	1.26 (3.21)	1.06 (0.28)	0.567*

*Dopamine D3 receptor signal intensity assessed by western immunoblotting. Non-significantly lower D3R protein levels were seen in the NAc of PD+DDS. PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs. Significant results in bold. Results expressed in median values and interquartile ranges. *Mann-Whitney U test.*

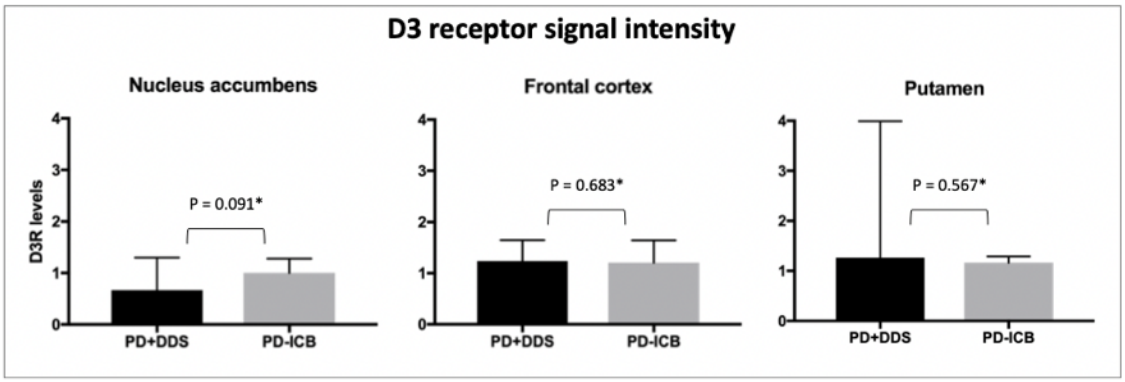


Figure 18. Comparison of D3 receptor signal intensity between PD patients with DDS (PD+DDS) and PD controls (PD-ICB).

*No differences were seen. The y axis represents signal intensity normalised for beta-acting and for the optimal internal control. Results expressed in median and interquartile ranges. *Mann-Whitney U test.*

5.3.5 Assessment of Lewy pathology and Alzheimer's disease neuropathological changes

Lewy pathology and Alzheimer's disease neuropathological changes were assessed in 22 PD+DDS and 29 PD-ICB. The majority of patients were classified as Braak stage 6 (Lewy pathology reaching neocortex and premotor areas with mild changes in primary sensory and motor cortex) and the remaining as stage 5 (Lewy pathology reaching high order sensory association areas of the neocortex and prefrontal neocortex) with no significant differences between groups. Cortical Lewy pathology assessment using the McKeith criteria revealed that all cases had either limbic or neocortical pathology with no differences according to the presence of DDS (table 29 on page 144).

Alzheimer's disease pathology was also analysed. No differences were seen in the Braak and Braak and Thal staging systems. Similarly, the CERAD and NIA-AA scores did not differ between groups, showing absent or low levels of Alzheimer's disease neuropathological changes in the majority of cases (table 29).

Table 29. Assessment of Lewy pathology and Alzheimer's disease neuropathological changes

	PD+DDS N = 22	PD-ICB N = 29	p value
Braak Lewy pathology staging	5: 22.7% 6: 77.3%	5: 3.4% 6: 96.5%	0.073*
McKeith criteria of cortical Lewy pathology	Limbic: 22.7% Neocortical: 77.3%	Limbic: 6.9% Neocortical: 93.1%	0.216*
Thal staging of beta amyloid deposition	0: 36.4% 1: 22.7% 2: 13.6% 3: 13.6% 4: 9.1% 5: 4.5%	0: 37.9% 1: 17.2% 2: 17.2% 3: 10.4% 4: 13.8% 5: 3.5%	0.983**
Braak and Braak tau staging	0: 18.2% 1: 40.9% 2: 22.7% 3: 9.1% 4: 9.1%	0: 13.8% 1: 51.7% 2: 27.6% 3: 6.9% 4: 0%	0.510**
CERAD score of neuritic plaques	0: 59.1% 1: 18.2% 2: 22.7% 3: 0%	0: 58.6% 1: 24.2% 2: 13.8% 3: 3.4%	0.675**
NIA-AA score of Alzheimer's disease neuropathological changes	Low: 50% Intermediate: 13.6% Not: 36.4%	Low: 58.6% Intermediate: 10.3% Not: 31.1%	0.400**

*Assessment of Lewy pathology and Alzheimer's disease neuropathological changes. PD+DDS – patients with PD and DDS; PD-ICB – PD patients without ICBs. Results expressed in proportions. *Fisher's exact test; **Chi-square test.*

5.4 Discussion

This is the first post mortem study of alpha-synuclein, D2R and D3R levels in PD+DDS. In line with previous research in ICBs (Weintraub et al., 2010a), the study population was composed mostly of males with early onset PD. The disease duration, slightly more than 20 years, was higher than that described in a general population of PD patients (Fahn et al., 2011b), corroborating previous findings that younger patients have slower disease progression (Wickremaratchi et al., 2009).

The first formal description of DDS was published by our centre in the year 2000 (Giovannoni et al., 2000), and the increased research interest in this ICB dating back many years allowed the inclusion of a significant number of patients with DDS. Multiple ICBs were seen in approximately 40% of patients, similar to a previous finding from a longitudinal study (Antonini et al., 2017).

A similar proportion of patients were exposed to DA in both groups. There was a trend for higher peak DA dose and higher DA dose at death in the PD+DDS group that did not reach significance. Previous research has identified DA as the strongest risk factor for ICBs in general (Averbeck et al., 2014), but the main risk factor for DDS is the use of levodopa (O'Sullivan et al., 2009). Therefore, the lack of differences in DA is likely a consequence of the inclusion of patients with DDS. This could also explain the higher total dopaminergic treatment dose seen in PD+ICB, as patients with DDS tend to use dopaminergic medication in excess of what is needed to control motor symptoms (O'Sullivan et al., 2009).

There is an asymmetry of striatum involvement in PD, with the dorsal parts being more severely affected compared to the ventral (Kish et al., 1988). As a consequence of the nigral degeneration associated with PD, there is reduction of TH in the striatum which correlates with disease duration, initially in the putamen, followed by the caudate and eventually the NAc (Jellinger, 2011). This pattern of progression was reproduced in the present study, where TH levels were highest in the NAc, followed by the caudate and the putamen. The fact that the ventral striatum tends to be affected later in the disease course led researchers to postulate that ICBs are a consequence of overstimulation of a

relatively preserved reward pathway by dopaminergic medication. This observation is supported by the dopamine overdose hypothesis, whereby the doses of levodopa needed to treat PD motor symptoms could overdose relatively intact dopaminergic structures and lead to functional disruption (Gotham et al., 1988).

Alpha-synuclein pathology reaches the neostriatum at Braak stage III and increases with PD progression (Mori et al., 2008). Contrary to the TH analysis, there was no gradient of alpha-synuclein staining between the NAc, dorsal putamen and caudate when both groups were analysed together. Comparison between groups, however, showed that PD+DDS had lower alpha-synuclein load in the NAc compared to PD-ICB. It is still under debate whether Lewy pathology is a direct consequence of the pathological process or an epiphenomenon (Jellinger, 2011) but the fact that the NAc was the only region with different levels of alpha-synuclein points to an important role of this structure and of alpha-synuclein pathology in the genesis of DDS. It is unlikely that differences in disease progression were behind the lower alpha-synuclein levels as both groups had similar disease duration and Lewy pathology staging, and TH levels in the NAc did not differ. It is possible that individual susceptibility is behind the lower levels of aggregated alpha synuclein found in patients with DDS, however, further studies are needed to answer this question.

Alpha-synuclein is a negative regulator of dopamine release as suggested by studies with cultured neurons and animal modes reporting inhibition of vesicle exocytosis by overexpression of this molecule (Abeliovich et al., 2000, Nemani et al., 2010). Although these studies did not consider the abnormally aggregated form of alpha-synuclein seen in PD, they may offer an explanation for how lower levels of alpha-synuclein could lead to excessive dopaminergic stimulation. Conversely, higher alpha-synuclein levels in PD-ICB would result in less dopaminergic stimulation that would be protective against DDS. Additionally, lower alpha-synuclein pathology levels in the NAc suggests a better-preserved ventral striatum, providing further evidence to support the dopamine overdose hypothesis as an explanation for ICBs.

D2R are widely expressed throughout the striatum (Hurd et al., 2001) and have been shown to be downregulated in the initial stages of PD (Antonini et al., 1997) and to normalise following chronic exposure to levodopa (Luquin-Piudo and Sanz, 2011). No significant differences in D2R levels were seen between groups, in line with a previous PET study involving PD patients with impulse control disorders (Payer et al., 2015). The fact that PD+DDS had non-significantly lower levels of D2R in the NAc coupled with the trend for higher peak and end DA doses could suggest that the lack of differences in D2R levels is an artefact of the small sample size, as downregulation of D2R has been shown to occur with DA use (Antonini et al., 1994, Payer et al., 2014). However, since the trend for lower D2R levels was only seen in the NAc this should be interpreted with caution.

Upregulation of D3R has been described in animal models after exposure to drugs of abuse and levodopa (Payer et al., 2014) and in the NAc of individuals following death from cocaine overdose (Mash and Staley, 1999). However, functional neuroimaging studies in humans with behavioural and drug addiction have consistently shown reduced D2R/D3R availability, which has been attributed to excessive synaptic dopamine (Payer et al., 2014). The expression of D3R in the NAc is regulated by the release of brain-derived neurotrophic factor from dopaminergic fibres, a possible explanation for how PD related degeneration could influence D3R levels (Guillin et al., 2001). Although D3R density does not appear to be altered by disease progression in animal models of PD (Luquin-Piudo and Sanz, 2011), a contradictory finding from a post mortem study has been published. The authors reported reduction of D3R in the striatum of PD patients compared to healthy controls, but reduction in the NAc was only seen after 10 years of disease progression (Ryoo et al., 1998).

In PD, D3R levels have been assessed in PET studies involving PD+ICB and post mortem studies of PD-ICB. PET studies reported reduced uptake of the tracer in the ventral striatum of patients with different types of ICBs. The interpretation of these findings differs according to the study methodology. Two studies have assessed patients after stimuli presentation, one examined patients with DDS after levodopa intake (Evans et al., 2006), and the other patients with diverse ICBs after presentation of visual cues (O'Sullivan et al.,

2011). The reduction in tracer binding seen in both studies is most likely a consequence of excessive dopamine release to stimuli, which would fit with the dopamine overdose hypothesis. Other PET studies, however, assessed patients with pathological gambling (Steeves et al., 2009) and PD with impulse control disorders (Payer et al., 2015) at baseline, without stimulus presentation. In this case, reduced tracer binding does not necessarily mean increased dopaminergic tone, it could be a consequence of reduced expression of dopamine receptors (Stark and Claassen, 2017). Only one of these studies used a highly selective D3R tracer, whereby the authors reported lower binding of the tracer in the limbic striatum, attributed to excessive synaptic dopamine (Payer et al., 2015). Since patients were assessed without levodopa, an alternative explanation is that the reduced tracer uptake is a consequence of lower D3R availability in the limbic striatum. Although no patients with DDS were included in that study, there appears to be a common hedonic representation of ICBs in the brain as different behavioural addictions are associated with similar pathophysiological findings (O'Sullivan et al., 2011), allowing extrapolation of these results to our study population. The results of the present study suggest that DDS is not associated with changes in NAc D3R levels, corroborating excessive dopamine release as an explanation for lower ventral striatum tracer binding reported in PET studies. However, it is possible that the sample size was not large enough to detect subtle differences.

Midbrain D2/D3 auto-receptors are able to modulate striatal dopamine levels after reward and the binding potential of these receptors has been negatively correlated with impulsivity (Buckholtz et al., 2010). Reduced D2/3 receptors in the midbrain caused by PD degeneration could, therefore, contribute to excessive ventral striatal dopamine and DDS. Future studies assessing midbrain auto-receptors are needed to answer this question.

Braak and McKeith staging showed that both groups were at similar stages of PD progression and cortical Lewy pathology. Alzheimer’s disease pathology also did not differ and was generally low in both groups. It has been shown that individuals with early onset PD have lower density of cortical Lewy pathology and less Alzheimer’s disease pathological changes (Halliday and McCann, 2010), which is in line with our results. The similar degrees of Lewy and

Alzheimer's pathology offer additional support for the hypothesis that our findings were not a consequence of different levels of neurodegeneration.

There are limitations to this study. Clinical data was analysed retrospectively, which is a problem inherent in brain bank studies. All patients were seen by specialists throughout disease progression and clinical data was thorough, minimising this issue. Furthermore, ICBs are usually under-reported (Perez-Lloret et al., 2012b) and this increases the risk of false negatives in the control group. To minimise this problem our controls were selected consecutively starting with more recent donations, when clinicians were more aware of ICBs. Lastly, the lack of a control group without neurodegenerative disease limits the generalisation of our findings.

5.5 Conclusion

This is the first post mortem study to assess alpha-synuclein pathology, TH reactivity, D2R and D3R levels in PD+DDS. Patients with DDS showed reduced alpha-synuclein load in the NAc compared to controls pointing to an important role for this structure in the genesis of behavioural addictions. Dopamine overdose could be motivated by lower Lewy pathology levels and PD treatment, resulting in an increased dopaminergic tone in a relatively preserved ventral striatum, ultimately leading to the development of DDS. This novel finding needs to be replicated by future studies.

Future research should assess PD patients in different stages of disease progression, include patients with other types of ICBs, analyse the influence of genetic polymorphisms in the expression of D2R and D3R and study additional brain areas of the dopaminergic reward pathway, such as the ventral tegmental area and the subiculum of the hippocampus.

Summary of findings

In the longest follow up study of PD+ICB to date, 46 patients were examined eight years after initial assessment. All but one participant experienced partial or complete improvement of the abnormal behaviour. However, 58% of them still had ICBs at the end of the follow up period, a lower remission rate than previously reported. Despite the most common therapeutic measure being cessation of DA, 40% of patients were still using oral/transcutaneous DA at the end of the follow up period, which could be explained in part by the development of DAWS in some subjects. Dopaminergic treatment dose was higher in the last visit, probably as a consequence of disease progression and increased medication requirements by patients. Corroborating previous findings, ICBs were associated with depression and worse quality of life but were not associated with increased risk of cognitive impairment. Although reduction of dopaminergic medication is considered the gold standard treatment of ICBs, for a significant proportion of patients it did not guarantee long term remission. Considering the possibility of long-term sensitisation, patients with remitted ICBs are at risk of recurrence during future treatment adjustments required for disease progression. Therefore, once a PD patient develops ICBs, close vigilance is required throughout the whole disease course, after remission and, particularly, after increases in dopaminergic treatment.

Another study looked into the clinical features of CSB in PD. CSB is an ICB that is particularly difficult to diagnose because of the sensitive nature of sexual behaviour. PD+ICB who participated in 3 previous research projects at the National Hospital for Neurology and Neurosurgery underwent a thorough clinical assessment followed by review of hospital notes. CSB was more frequently seen in males and appeared earlier than other ICBs. Individuals with CSB were more likely to develop multiple ICBs with negative impact on mental well-being and quality of life. For the first time, higher doses of levodopa were associated with CSB. The main clinical implication arising from this finding is that patients using higher doses of levodopa should be carefully screened for CSB.

A retrospective analysis of PD patients with DDS who donated their brains to the QSBB was the first study to investigate the outcome of DDS until death. A search on the QSBB archives revealed that 193 donations with pathologically confirmed PD were received between 2005 and 2016. A higher prevalence of DDS (8.8%) than previously reported was found. Furthermore, DDS was associated with male sex, younger age at PD onset, longer disease duration and levodopa-induced dyskinesias, corroborating previous research. Treatment strategies included reduction of levodopa, reduction/cessation of DA and initiation of infusion therapies. Remission rate was approximately 50%. Patients who failed to achieve remission were exposed to higher peak DA dose, a novel finding that needs to be replicated by future studies.

Despite punding being initially described in a PD patient in 1994, little is known about the cognitive and neuropsychiatric profile of patients who develop this behavioural abnormality. Forty-seven individuals with PD and punding were compared to 25 PD patients without punding or other ICBs. Patients with punding showed increased self-rated impulsivity and anxiety levels, higher prevalence of PD-related motor fluctuations and worse frontal lobe function in comparison to PD-ICB. Reduction in DA dose occurred in both groups, but patients with punding were submitted to a significantly larger reduction. These results offer an interesting insight into the mechanisms associated with punding. Higher dopaminergic stimulation in individuals with reduced inhibitory control could be the mechanism driving this behavioural abnormality.

Preliminary data suggests that apomorphine infusion carries less risk of triggering ICBs in PD compared to other DA. This could be a consequence of its pharmacological profile as it binds mainly to D1R and D2R, akin to levodopa and opposed to oral/transcutaneous DA, which have stronger affinity for D3R. In an attempt to assess apomorphine's proclivity to trigger ICBs, a retrospective analysis of all patients with PD actively using apomorphine via continuous infusion in the years of 2013 and 2014 at the National Hospital for Neurology and Neurosurgery, London, UK, was conducted. Twenty-eight patients were included with mean age at PD onset of 51 years and approximately 18 years of disease duration. Five patients discontinued the treatment and nearly 90% had at least one side effect. Twelve patients had ICBs before being prescribed

apomorphine, among these, six had complete remission and no recurrence after starting apomorphine, and six were still symptomatic when apomorphine infusion started (4 improved and 2 did not experience worsening). Only one patient among the 16 with no previous history of ICBs developed a behavioural addiction: mild compulsive eating during concomitant use of levodopa. The data from this analysis suggests that apomorphine has indeed lower risk of triggering ICBs, indicating that it is a viable treatment option for patients with ICBs who failed to achieve good symptomatic control after cessation of oral/transcutaneous DA.

Saccadic abnormalities have been previously reported in PD patients and healthy individuals with high impulsivity levels. To the present date, no studies have assessed eye movements of PD+ICB. Fifteen PD+ICB were assessed using a pro-saccades and an anti-saccades task and compared to 15 PD-ICB matched by age at PD onset and PD duration and 15 HC matched by age. No differences were found in the pro-saccades task confirming previous findings that automatic saccades are preserved in PD. In the anti-saccades task PD+ICB made hypometric voluntary saccades compared to healthy participants and a significantly higher number of direction errors compared to both PD-ICB and healthy individuals, showing an inability to suppress automatic saccades. One important conclusion from this work is that saccadic assessment has the potential to evolve into a marker of ICBs to guide therapeutic decision in patients at risk, provided this finding is confirmed by future studies. This would have a significant impact in clinical care as ICBs are commonly under-reported.

Two main theories have been postulated to explain ICBs in PD: excessive dopaminergic release leading to overstimulation of a relatively preserved ventral striatum; and excessive stimulation of D3R, abundant in the limbic striatum. The former is supported by observations from PET studies and the latter by clinical research showing a strong association between ICBs and DA. Only one PET study has used tracer that binds specifically to D3R in PD+ICB and found no upregulation of this receptor. To date, no post mortem studies with individuals who were diagnosed with PD and ICBs in life have been conducted. Brain samples from 24 individuals with PD+DDS from the QSBB were compared to 29 PD-ICB, matched by sex, age at PD onset, PD duration and age at death.

Immunohistochemistry techniques were used to assess alpha-synuclein and tyrosine hydroxylase levels in the NAc, dorsal putamen and dorsal caudate. Western immunoblotting was used to compare levels of alpha-synuclein, D2R and D3R in the NAc, dorsal putamen and inferior frontal cortex. Patients with DDS had significantly lower levels of alpha-synuclein in the NAc compared to controls. D2R and D3R levels did not differ. These findings suggest an important role for the NAc in the expression of ICBs. Individual susceptibility to Lewy pathology could result in lower levels of aggregated alpha-synuclein ultimately leading to excessive dopaminergic stimulation of dopamine receptors in the ventral striatum, supporting the dopamine overdose hypothesis as an explanation for ICBs.

Directions for future research

Further studies are needed to confirm the novel findings reported in this thesis: the association between CSB and higher doses of levodopa; higher peak DA dose and lower remission rate of DDS; frontal dysfunction and punding behaviour; increased anti-saccadic direction error rate in PD+ICB; and lower levels of alpha-synuclein in the NAc of PD+DDS.

Future prospective clinical studies are needed to compare the efficacy of different treatment strategies and the outcomes of specific types of ICBs in PD patients. Furthermore, apomorphine safety needs to be validated by randomised clinical trials and/or prospective clinical studies.

One promising methods of identifying PD+ICB were explored in this thesis: anti-saccadic direction error rate. If this finding is confirmed by other authors, the feasibility of creating a bedside version of the anti-saccades test in order to identify individuals at risk or who have already developed ICBs should be tested.

D3R should also be investigated in patients at different stages of disease progression to assess how protein levels of this receptor in the NAc are affected by disease progression, and whether pre-morbid differences are associated with ICBs. Another important question that could be answered by genome wide association studies is whether genetic polymorphisms of D3R influence the risk of ICBs in PD. Study of additional brain areas of the dopaminergic reward pathway, such as the ventral tegmental area and the subiculum of the hipoccampus, are also required to understand their roles in behavioural addiction. Other neurotransmitters could be implicated in ICBs and the study of opioid and serotoninergic receptors could provide important insights into the pathophysiology of ICBs. Finally, separate analysis of the shell and core of the NAc could contribute to our understanding of the different types of ICBs as research with animal models have associated different regions of the NAc with different behavioural addictions.

Acknowledgements

I would like to thank Prof Tom Warner for the support received during the PhD programme. It made a great difference to an otherwise stressful period to have a supervisor that was always available, caring, knowledgeable, kind and always in good spirits. I would also like to thank my co-supervisor, Dr Atbin Djamshidian, for being a constant presence throughout my PhD. Atbin was the one who motivated me to enter the impulsive compulsive behaviours field and I shall be always grateful for that.

A special thanks to Prof Andrew Lees for being a source of inspiration and for the important contribution in every chapter of this thesis. I am grateful to Prof Janice Holton for the teachings and invaluable advice on neuropathology, and to Dr Rohan de Silva for the friendship and expert advice on western blotting. I would not be able to finish chapter 5 without the help from Kate Strand and Bimali Hapuarachchi. I will always cherish their friendship and kindness in the lab. A special thanks to Karen Shaw who helped me navigate through every stage of my PhD, from ethics approval and recruitment to dissemination of results.

I have never felt more welcome than during my studies at the Queen Square Brain Bank and Reta Lila Weston Institute, and for that I would like to thank all the staff, specially my office mates Eduardo de Pablo-Fernandez, Helen Ling, Alastair Noyce, Daniela Hansen and Sam Shribman. Helen, Eduardo and Alastair, particularly, made me feel at home since my first day at the Brain Bank. I am also grateful to Iliyana Komsiyska for being always there and always kind.

I am grateful for the expert help received from Robert Courtney, Geshanti Hondhamuni, Linda Parsons, Bridget Benson, Christina Murray, Nanet Willumsen, Tammaryn Lashley, Abi Li, Sandrine Foti and Charlie Arber. I thank Cathy Magee and Katia Crowley for the amazing support received at the National Hospital for Neurology and Neurosurgery; as well as Yvonne Mwelwa, Maureen Lacey and Janet Connellan.

It has been a privilege to receive support from brilliant collaborators including Prof Eileen Joyce, Dr Sean O'Sullivan, Dr Diego Kaski, Prof Thomas Foltynie, Prof Huw Morris, Prof Kailash Bhatia, Prof Patricia Limousin, Dr Prasad Korlipara, Dr Andre Zacharia and Dr Philipp Mahlknecht.

I am grateful to my sponsor, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), for the financial support received during my studies; and to the Reta Lila Weston Institute of Neurological Studies and the Queen Square Brain Bank for Neurological Disorders for supporting my research.

At last but not least I would like to thank my wife, Candice, for the unconditional support, without which I would not be able to undertake this project; my parents and siblings, for supporting me from overseas; and Caetano for keeping me focused.

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